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CONTENTS

Papers

- Synthesis of Methyl Ester of 7-Oxo-11-nordrim-8-en-12-oic Acid, a Metabolite of the Fungus *Lepista glaucocana* (Bres.) Singer 505
S Janaki & G S R Subba Rao*
- Steroids & Related Studies: Part 82—Chandonium Related Azasteroidal Neuromuscular Blockers 508
Harkishan Singh*, Rakesh Kumar Gupta & Tilak Raj Bhardwaj
- Metal Hydride Catalyzed Rearrangement of Bicyclic Carbinols: Formation of an Unexpected Lactone during an Attempted Oxy-Cope Rearrangement. 513
S P Ganesh Raj, S Janardhanan & K Rajagopalan*
- Unusual Products of Catalytic Hydrogenation of 2,2-Dimethyl-3-phenyl-4(*p*-Hydroxyphenyl)-7-methoxychromene 516
Indra Sharma, Suprabhat Ray* & A H Ansari
- Oxidation of Triterpenoids: Part VIII—Oxidation of Taraxerone with Selenium Dioxide in *t*-Butanol. 520
Bhim Prasad Pradhan*, Satyajit Chakraborty & Peter Weyerstahl
- Synthesis of 4-(2-Benzofuranyl)coumarins 524
A R Deshpande, U K Joshi & M V Paradkar*
- Use of Ferric Chloride in Carbohydrate Reactions: Part V—Acetolysis of Methyl Hexopyranosides Using Ferric Chloride in Acetic Anhydride. 527
Falguni Dasgupta, Prem P Singh & Harish C Srivastava*
- Preparation & Cleavage of Some Cyclopropane Derivatives 530
Ranjan Kumar Podder, Ranjit Kumar Sarkar & Suvas C Ray*
- Regioselective Reactions of Tetra- & Penta-substituted Pyrroles 537
Anita Mukherjee, V L Sharma, M Seth & A P Bhaduri*
- Synthesis & Biological Activities of Isoxazolo[5,4-*d*]pyrimidinylloxymethyl-thiadiazoles, -oxadiazoles & -triazoles 542
Vasudeva A Adhikari & Virupax V Badiger*
- Reaction of 3-Hydrazino-5,6-diphenyl-1,2,4-triazine with Unsymmetrical 1,3-Bicarbonyl Compounds: Synthesis of Some New 3-(3',5'-Disubstituted pyrazol-1'-yl)-5,6-diphenyl-1,2,4-triazines & Their Antimicrobial Activity 548
R M Abdel-Rahman
- Notes 554
An Efficient Route for γ -Alkyl- γ -butyrolactones
M K Gurjar* & A V Purandare

Continued overleaf

Synthesis of 2-Formyl-6-hydroxymethyl-4-methyl-4,5,6,7-tetrahydrobenzo[<i>b</i>]furan: A Key Intermediate for Analogues of Homoprostacyclines	556
B Veeraiah, T Ratna Vani & R Balaji Rao*	
Convenient One-pot Synthesis of (<i>Z</i>)-4-Benzoyloxy-2-buten-1-ol	558
S V Hiremath*, D R Reddy & M Anil Kumar	
Bridged Hydroquinolines	559
S N Balasubrahmanyam* & B Jeyashri	
Synthesis of Indazolo[2,3- <i>a</i>]quinolines	563
V Padma Reddy & K Kondal Reddy*	
Studies in Heterocyclisation of Michael Products from Isoxazoles.	565
V Venkateshwarlu, A Krishnamurthy & C Janakiram Rao*	
Reaction of N-Alkyl/Aralkylisatoic Anhydrides with Aroylhydrazines: Formation of 1,3,4-Oxadiazoles & 1,4-Dihydro-5 <i>H</i> -1,3,4-benzotriazepin-5-one	568
Ch K Reddy, P S N Reddy & C V Ratnam*	
Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Synthesis of Imidazo[2,1- <i>b</i>]thiazoles, Imidazo[2,1- <i>b</i>][1,3]thiazin-4(3 <i>H</i>)-one & Imidazo[2',1':2,3]thiazolo[4,5- <i>b</i>]quinoxaline	570
Jag Mohan*, G S R Anjaneyulu & (Ms) Kiran	
Reaction of 4-Aryl-2-hydrazinethiazoles with Ethyl Acetoacetate: A Reinvestigation.	573
S P Singh*, Subhash Sehgal, P Diwakar & R K Vaid	
A Novel Synthesis of <i>s</i> -Triazolo[3,4- <i>b</i>][1,3,4]thiadiazole Derivatives	576
Bharati Mishra, R Ali & Nizamuddin*	
Synthesis of a Novel 1,4-Thiazine System	578
J Shailja Rao*, Parvathi Neelakantan & S Nagabhushan Rao	
A Convenient Synthesis of 2-Methyl/ethyl- Δ^1 -pyrrolines	580
S Ananthapadmanabhan*, T K Raja, V Srinivasan & A Simon	
A Versatile Synthesis of 2-Aryl-3, 4-dihydro-4-oxobenzofuro[3,2- <i>d</i>]pyrimidines.	581
B Saida Reddy, A Panduranga Reddy & V Veeranagaiah*	
A Convenient Synthesis of Carbamazepine (Tegretol)	583
S Salman Ahmad*, Farrukh Hafeez, S Imtiaz Haider & Tariq Mahmood	
Stereoselective Synthesis of 5 α , 7 β -Dicyanocholestan-6-ones.	584
(Miss) Rubina Habib, Mashkoor Husain, Abul Fazal* & Mubarak Husain	
Base-catalysed Reaction of Formaldehyde with 1,3-Diaryl-1,3-propanediones	587
S J Joglekar & S D Samant*	
Use of Aluminium as a Friedel-Crafts Catalyst	589
F Akhter & M H Bahar*	
<i>o</i> -Phenanthroline Thiolester as a Reactive Acylating Reagent	590
Yoshio Ueno, R K Khare* & Makoto Okawara	
Reaction of Acetophenone with Potassium Hydroxide in Diethylene Glycol	592
Bhim Prasad Pradhan* & (Miss) Tandra Ray	

Studies on Rutaceae: Part VIII—Chemical Investigation on the Constituents of <i>Atalantia wightii</i> Tanaka, <i>Aegle marmelos</i> Correa ex Koen, <i>Ruta graveolens</i> Linn. & <i>Micromelum pubescens</i> Blume J Banerji*, A K Das, N Ghoshal & B Das	594
Isolation of 4,4'-Dimethoxy- <i>trans</i> -stilbene & Flavonoids from Leaves & Twigs of <i>Vitex negundo</i> Linn. J Banerji*, B Das, R Chakrabarty & H C Jha	597
Products Active on Mosquitoes: Part II – Synthesis of Biologically Active Diethers of 3,7-Dimethyl-1,8-octanediol A P Phadnis, Sarita A Patwardhan*, P V Powar & R N Sharma	597
Synthesis & Pharmacological Activities of 5-(Aminoacetyl-amino)-4-carbethoxy-1-phenyl-pyrazoles U S Pathak*, M B Devani, C J Shishoo, H H Patel, T P Gandhi & R B Patel	602

Authors for correspondence are indicated by (*)

Experimental Procedures	603
1. Synthesis of 3,7-Dimethyl-1,8-octanediol	603
2. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
3. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
4. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
5. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
6. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
7. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
8. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
9. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
10. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
11. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
12. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
13. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
14. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
15. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
16. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
17. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
18. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
19. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
20. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
21. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
22. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
23. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
24. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
25. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
26. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
27. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
28. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
29. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
30. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
31. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
32. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
33. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
34. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
35. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
36. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
37. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
38. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
39. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
40. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
41. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
42. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
43. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
44. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
45. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
46. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
47. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
48. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
49. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
50. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
51. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
52. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
53. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
54. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
55. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
56. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
57. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
58. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
59. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
60. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
61. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
62. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
63. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
64. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
65. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
66. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
67. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
68. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
69. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
70. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
71. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
72. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
73. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
74. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
75. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
76. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
77. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
78. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
79. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
80. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
81. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
82. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
83. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
84. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
85. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
86. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
87. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
88. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
89. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
90. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
91. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
92. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
93. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
94. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
95. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
96. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
97. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
98. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
99. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603
100. Synthesis of 3,7-Dimethyl-1,8-octanediol diethers	603

Author Index

Abdel-Rahman R M	548	Okawara Makoto	590
Adhikari Vasudeva A	542	Paradkar M V	524
Ahmad S Salman	583	Patel H H	602
Akhter F	589	Patel R B	602
Ali R	576	Pathak U S	602
Ananthapadmanabhan S	580	Patwardhan A	600
Anjaneyulu G S R	570	Phadnis A P	600
Ansari A H	516	Poddar Ranjan Kumar	530
Badiger Virupax V	542	Powar P V	600
Balasubrahmanyam S N	559	Pradhan Bhim Prasad	520,592
Banerji J	594,597	Purandare A V	554
Bhaduri A P	537	Raj S P Ganesh	513
Bhardwaj Tilak Raj	508	Raja T K	580
Chakrabarty R	597	Rajagopalan K	513
Chakraborty Satyajit	520	Rao C Janakiram	565
Das A K	594	Rao G S R Subba	505
Das B	594,597	Rao J Shailja	578
Dasgupta Falguni	527	Rao R Balaji	556
Deshpande A R	524	Rao S Nagabhushan	578
Devani M B	602	Ratnam C V	567
Diwakar P	573	Ray Suprabhat	516
Fazal Abul	584	Ray Suvas C	530
Gandhi T P	602	Ray Tandra	592
Ghoshal N	594	Reddy A Panduranga	581
Gupta Rakesh Kumar	508	Reddy B Saida	581
Gurjar M K	554	Reddy Ch K	568
Habib Rubina	584	Reddy D R	558
Hafeez Farrukh	583	Reddy K Kondal	563
Haider S Imtiaz	583	Reddy P S N	568
Hirenath S V	558	Reddy V Padma	563
Husain Mashkooor	584	Samant S D	587
Husain Mubarak	584	Sarita	600
Jag Mohan	570	Sarkar Ranjit Kumar	530
Janaki S	505	Sehgal Subhash	573
Janardhanan S	513	Seth M	537
Jeyashri B	559	Sharma Indra	516
Jha H C	597	Sharma R N	600
Joglekar S J	587	Sharma V L	537
Joshi U K	524	Shishoo C J	602
Khare R K	590	Simon A	580
Kiran	570	Singh Harkishan	508
Krishnamurthy A	565	Singh Prem	527
Kumar M Anil	558	Singh S P	573
Mahmood Tariq	583	Srinivasan V	580
Mishra Bharati	576	Srivastava Harish C	527
Mukherjee Anita	537	Ueno Yoshio	590
Neelakantan Parvathi	578	Vaid R K	573
Nizamuddin	576	Vani T Ratna	556
		Veeraiah B	556
		Veeranagaiah V	581
		Venkateshwarlu V	565
		Weyerstahl Peter	520

Synthesis of Methyl Ester of 7-Oxo-11-nordrim-8-en-12-oic Acid, a Metabolite of the Fungus *Lepista glaucocana* (Bres.) Singer

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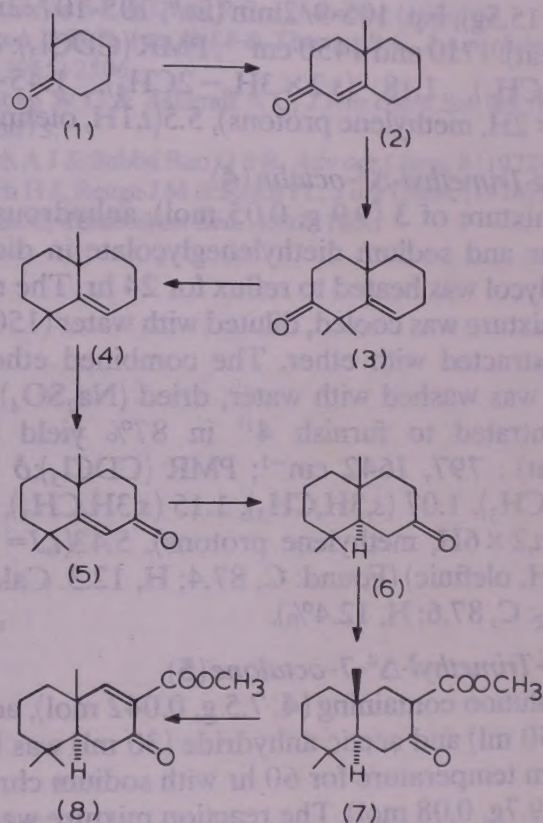
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Synthesis of methyl ester of 7-oxo-11-nordrim-8-en-12-oic acid (**8**) is described.

The culture fluid of *Lepista glaucocana* (Bres.) Singer was reported¹ to contain four acetylenic acids and a nitrile enol ether. Recently Thaller *et al.*² isolated the methyl ester of 7-oxo-11-nordrim-8-en-12-oic acid (**8**) as the major component from the terpene fraction of the above culture and deduced its structure from analytical and spectral data. We now report the synthesis of this component from 2-methylcyclohexanone and confirm the proposed structure.

As part of a synthetic programme³ on calyone, calyenone and precalyone, the three diterpenoids⁴ from *Roylea calycina* having antitumor properties, we had occasion to prepare the key intermediate 1,1,4a-trimethyl-*trans*-7-decalone (**6**) from 2-methylcyclohexanone (**1**) in five steps. Thus reaction of **1** with methyl vinyl ketone followed by cyclization in the presence of PTS in refluxing benzene afforded the unsaturated ketone⁵ (**2**) in 61% yield. Alkylation of **2** with methyl iodide in the presence of KOBu/^tBuOH gave⁶ the saturated ketone (**3**), which was subjected to reduction under Huang-Minlon conditions⁷ to yield 1,1,4a-trimethyl- Δ^8 -octalin (**4**) (87%). Oxidation of **4** with sodium chromate-acetic acid resulted⁸ in the unsaturated ketone (**5**), which was reduced with lithium in liquid ammonia to give the saturated ketone (**6**), as the only component. Metal-ammonia reduction of unsaturated ketones is known⁹ to produce thermodynamically the most stable isomer.

Reaction of **6** with dimethyl carbonate in the presence of sodium hydride afforded the β -keto ester (**7**) in 70% yield. Introduction of the 8(9) double bond in **7** using phenylselenenyl chloride and hydrogen peroxide¹⁰ led to the unsaturated keto ester (**8**) in 80% yield. The spectral data (UV, IR, PMR, CMR) of **8** were identical with the reported data, although direct comparison of the synthetic sample could not be made with the natural material.



Experimental Procedure

IR spectra were recorded on a Perkin-Elmer model 781 spectrophotometer, UV spectra on a Shimadzu model-190 double beam spectrophotometer and PMR spectra on Varian T-60, JEOL FX-90Q or Bruker WH-270 FT spectrometer using TMS as an internal standard. Mass spectra were recorded on JEOL MS-DX 303 with a built-in direct inlet system.

10-Methyl-1(9)-octalone (2)

To a mixture of 2-methylcyclohexanone (1,28 g) and 3N ethanolic sodium ethoxide (1.5 ml), maintained at -10°C under nitrogen atmosphere, was added methyl vinyl ketone during 3 hr. The reaction mixture was allowed to stand at -10°C for another

6 hr and the cold mass was diluted with brine and ether. The ethereal extract was dried and distilled to give a liquid which was refluxed with PTS (500 mg) in dry benzene (250 ml) for 3 hr. The benzene extract was washed with water, dried and the solvent was removed to yield **2** (25 g, 61% yield), b.p. 115-20/3mm (lit.⁵ b.p. 102-10/2.5mm); IR (neat): 1670 and 1630 cm^{-1} ; PMR (CCl_4): δ 1.27 (s, 3H, $-\text{CH}_3$), 1.3-2.5 (complex, $6 \times 2\text{H}$, methylene protons), 5.5 (s, 1H, olefinic).

1,1,4a-Trimethyl- Δ^8 -3-octalone (**3**)

Compound (**2**, 16.4g, 0.1 mol) was allowed to react with potassium *t*-butoxide (28g, 0.25mol) and methyl iodide (26 ml, 4 equiv) to yield pure **3**, yield 80% (15.5g), b.p. 105-9/2mm (lit.⁶ 105-107/2mm); IR (neat): 1710 and 1450 cm^{-1} ; PMR (CDCl_3): δ 1.0 (s, 3H, CH_3), 1.18 (s, $2 \times 3\text{H}$, -2CH_3), 1.45-2.56 (m, $5 \times 2\text{H}$, methylene protons), 5.5 (t, 1H, olefinic).

1,1-4a-Trimethyl- Δ^8 -octalin (**4**)

A mixture of **3** (9.9 g, 0.05 mol), anhydrous hydrazine and sodium diethyleneglycolate in diethylene glycol was heated to reflux for 24 hr. The reaction mixture was cooled, diluted with water (150 ml) and extracted with ether. The combined ethereal phase was washed with water, dried (Na_2SO_4) and concentrated to furnish **4**¹¹ in 87% yield (8g); IR (neat): 797, 1642 cm^{-1} ; PMR (CDCl_3): δ 1.03 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.3-2.0 (m, $2 \times 6\text{H}$, methylene protons), 5.43 (t, $J = 3.52$ Hz, 1H, olefinic) (Found: C, 87.4; H, 12.3. Calc for $\text{C}_{13}\text{H}_{22}$: C, 87.6; H, 12.4%).

1,1,4a-Trimethyl- Δ^8 -7-octalone (**5**)

A solution containing (**4**, 7.5 g, 0.042 mol), acetic acid (50 ml) and acetic anhydride (30 ml) was kept at room temperature for 60 hr with sodium chromate⁸ (19.7g, 0.08 mol). The reaction mixture was diluted with water, neutralised with Na_2CO_3 and extracted with ether. The combined ethereal extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on silica gel. Elution with hexane-ethyl acetate (9:1) afforded **5** (5 g, 62% yield); IR (neat): 1670, 1600 cm^{-1} ; PMR (CDCl_3): δ 1.14 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.5-2.5 (m, $5 \times 2\text{H}$, methylene protons), 5.92 (s, 1H, olefinic) (Found: C, 81.2; H, 10.5. $\text{C}_{13}\text{H}_{20}\text{O}$ requires C, 81.2; H, 10.5%).

1,1,4a-Trimethyl-trans-7-decalone (**6**)

Lithium (109 mg, 3 equiv.) was added in small pieces with constant stirring to freshly distilled ammonia. The deep blue coloured solution was stirred for 5 min and the enone (**5**, 1 g, 5.2 mmol) in dry THF (5 ml) was added in drops. The mixture was

stirred for 30 min and quenched with solid ammonium chloride. Ammonia was allowed to escape and the residue was diluted with water. This was extracted with ether (3×50 ml) and the ethereal solution was washed with water, brine and dried (Na_2SO_4). Evaporation of ether followed by chromatography on silica gel with hexane-ethyl acetate (9:1) as eluant gave **6** (750 mg, 74.2% yield); IR (neat): 1710, 1390 cm^{-1} ; PMR (CDCl_3): δ 0.84 (s, 6H, $2 \times \text{CH}_3$), 1.12 (s, 3H, CH_3), 1.4-2.5 (m, 13H, methylene protons); MS: m/z 194 (81%, M^+), 179(32), 137(33), 123(91), 95(38), 81(55) and 69(100%) (Found: C, 80.3; H, 11.5. $\text{C}_{13}\text{H}_{22}\text{O}$ requires C, 80.4; H, 11.4%).

Methyl 7-oxo-11-nordriman-12-oate (**7**)

Sodium hydride (338 mg, 7.75 mmol, 55% dispersion in mineral oil, washed by decantation thrice with pet ether) was suspended in dry benzene (10 ml). Freshly distilled dry dimethyl carbonate (7 ml) was added, followed by the compound (**6**, 600 mg, 3 mmol) in dry benzene at 0°C under nitrogen atmosphere. The mixture was refluxed for 14 hr, cooled and excess sodium hydride was decomposed by addition of water. The solution was thoroughly extracted with ether, washed with 5% HCl, water, brine and dried (Na_2SO_4). Evaporation of the solvent gave a viscous liquid which on chromatography over silica gel and elution with hexane-ethyl acetate (9:1) afforded **7** (550 mg, 70% yield); IR (neat): 1746(w), 1720(w), 1680(s), 1620(m) cm^{-1} ; PMR (CDCl_3): δ 0.88 (s, 9H, 3CH_3), 3.74 (s, 3H, COOCH_3), 12.0 (s, 1H, enolic proton); MS: m/z 252 (35% M^+), 237(5), 221(7), 205(7), 192(6), 177(7), 168(10), 128(46), 124(29), 109(100) and 41(40) (Found: M^+ 252.1712. Calc for $\text{C}_{15}\text{H}_{24}\text{O}_3$: M^+ 252.1725).

Methyl 7-oxo-11-nordrim-8-en-12-oate (**8**)

To a stirred suspension of sodium hydride (125 mg, 2.9 mmol, 55% dispersion in oil, washed free of oil with 3×10 ml of pet ether) in dry THF (10 ml) under nitrogen atmosphere at 0°C was added dropwise a solution of **7** (290 mg, 1.15 mmol) in THF (2 ml) during 15 min. A solution of phenylselenenyl chloride (220 mg, 1.15 mmol) in THF (5 ml) was added rapidly and the reaction mixture was slowly added with stirring to a mixture of 50% ether-hexane (20 ml) containing saturated aq NaHCO_3 (10 ml). The aqueous layer was extracted with 50% ether-hexane (3×25 ml). The combined organic layer was washed with saturated brine solution (10 ml) and dried (Na_2SO_4). On evaporation of the solvent a viscous yellow coloured liquid was obtained.

To a stirred solution of the above selenide in methylene chloride (30 ml) was added 30% hydrogen peroxide (5 ml) during 10 min at $20-30^\circ\text{C}$. After

stirring for an additional 10 min at 25°C, the reaction mixture was diluted with methylene chloride (25 ml) and aq. sodium carbonate (10 ml). The aqueous layer was extracted with methylene chloride (3 × 25 ml). The combined organic layer was washed with brine and dried (Na₂SO₄). On evaporation of the solvent a liquid was obtained which was chromatographed over silica gel. Elution with hexane-ethyl acetate (3:2) afforded the pure **8** (230 mg, 80% yield); UV (EtOH): 226 nm (ϵ , 8810); IR(neat): 1745, 1720, 1688 cm⁻¹; PMR (CDCl₃): δ 0.88 (s, 3H, CH₃), 0.92 (s, 3H, CH₃), 1.14 (s, 3H, CH₃), 3.8 (s, 3H, COOCH₃), 7.34 (s, 1H, H-9-proton); ¹³C NMR (CDCl₃): δ 11.7(*q*), 18.3(*t*), 20.8(*q*), 32.0(*q*), 32.9(*s*), 36.04(*t*), 37.2(*s*), 37.4(*t*), 40.8(*t*), 49.4(*q*), 51.9(*d*), 128.8(*s*), 165.1(*s*), 166.8(*d*), 195.7(*s*); MS: *m/z* 250 (55% M⁺) 235(30), 219(53), 218(90), 208(38), 203(41), 191(35), 136(61), 127(88), 109(100) and 41(100) (Found: M⁺ 250.1568. Calc for C₁₅H₂₂O₃: M⁺ 250.1569) (Found: C, 71.9; H, 9.0. Calc for C₁₅H₂₂O₃: C, 72.0; H, 8.9%).

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Steroids & Related Studies: Part 82—Chandonium Related Azasteroidal Neuromuscular Blockers

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Modelled on clinically active chandonium iodide (1) different azasteroidal neuromuscular blockers have been designed. 17 β -Dimethylamino-3 β -pyrrolidino-5-androstene dimethiodide (HS-854) (2), having not the 17a-aza-D-homo system but extranuclear quaternary ammonium head with nearly equivalent steric placement, and the 17 β -dimethylamino-3 α -pyrrolidino-5-androstene dimethiodide (HS-1046) (dimethiodide of 6) have been synthesized. 17 β -Dimethylamino-3 β -pyrrolidino-5 α -androstane dimethiodide (HS-944) (7) is the dihydro analogue of HS-854 (2). The other modification, viz 6-hydroxymethyl-17 β -dimethylamino-3 β -pyrrolidino-5-androstene dimethiodide (HS-892) (13) has a sterically significant substituent at position-6 which should also alter hydrophilic-lipophilic balance. All the new bisquaternary steroids are active as neuromuscular blockers in the rat phrenic nerve diaphragm preparation. The structure-activity relationship has been discussed.

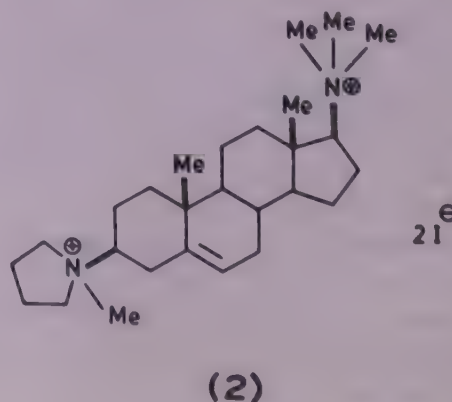
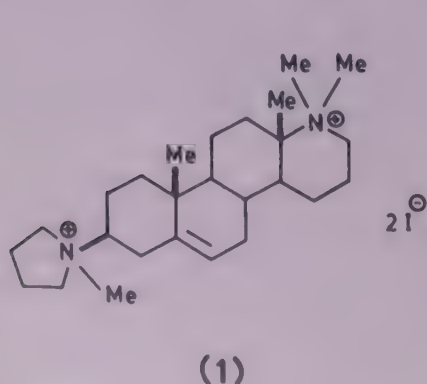
The interest in the design of new neuromuscular blocking agents continues¹ unabated. The studies on steroidal bisonium compounds has been rewarded by the discovery of some clinically effective drugs. Most of our own work has been on the preparation of analogues in which one or both of the cationic systems are present as part of the steroid ring skeleton²⁻⁶. One such compound chandonium iodide (HS-310), chemically 17a-methyl-3 β -pyrrolidino-17a-aza-D-homo-5-androstene dimethiodide (1)^{3,7} has particularly shown promise. Phase II clinical studies on it have been completed at the Central Drug Research Institute, Lucknow. In this paper we describe the studies on some of the new azasteroidal agents in which the quaternary nitrogen functions are extranuclear.

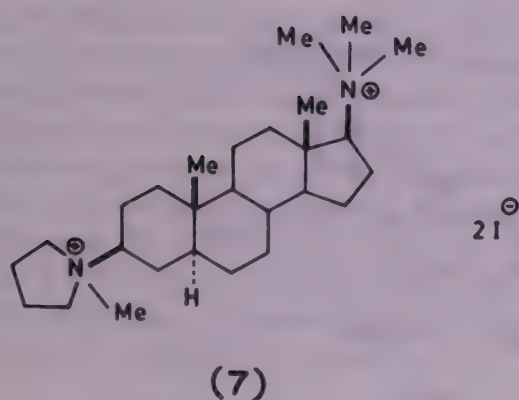
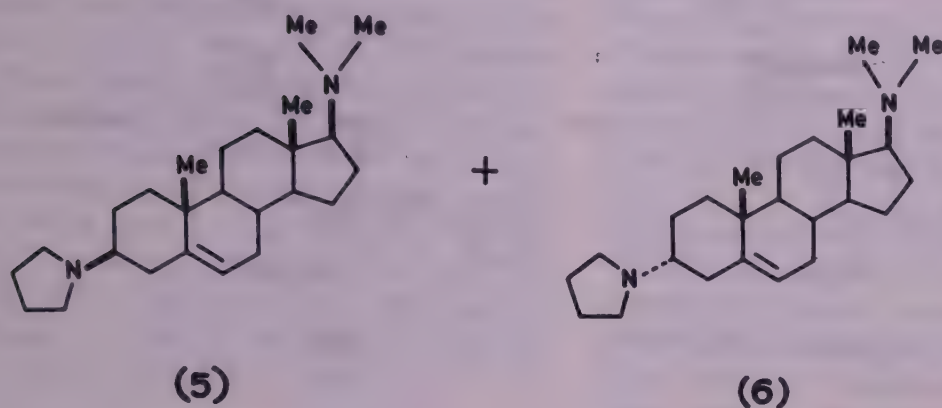
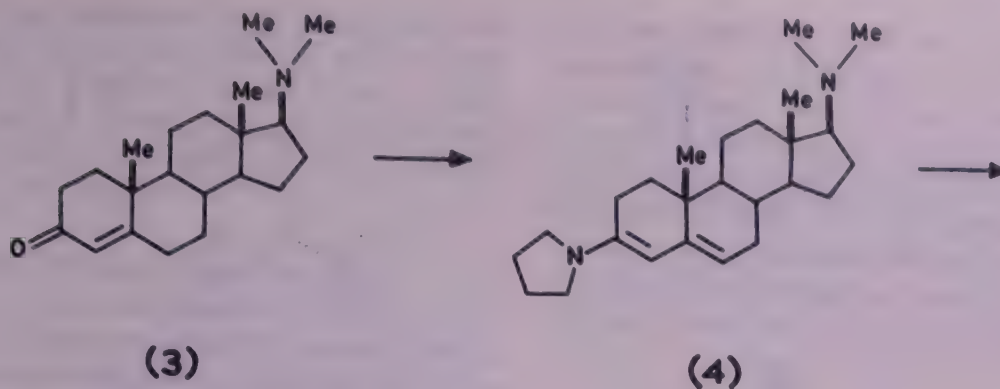
Considering chandonium (1) as a model it was visualized to prepare the analogue (2) where in place of nitrogen in ring-D extranuclear 17 β -quaternary nitrogen moiety is introduced.

17 β -Dimethylamino-4-androsten-3-one (3) was prepared from 17-oxo-5-androsten-3 β -yl acetate through oximation, sodiumpentanol reduction, methylation

and Oppenauer oxidation. The experimental conditions have been different from those used previously⁸. The α , β -unsaturated ketone (3) on treatment with pyrrolidine in methanol gave the enamine (4), which on sodium borohydride reduction gave 5; the 3 β -configuration in 5 being indicated on the basis of similar reported reductions⁹⁻¹¹. In addition there was obtained a small amount of another product which was considered to be the 3 α isomer 6. The tertiary amines 5 and 6 were treated with methyl iodide to yield the quaternary ammonium products HS-854 (2) and HS-1046 (dimethiodide of 6). The interonium distances through Dreiding models were found to be 1.13 nm and 0.996 nm, respectively, as compared with interonium distance of 1.029 nm in 1¹¹.

It was observed that the neuromuscular blocking activity of 5 α -dihydrochandonium iodide^{4,12} was one-half of that of 1. It was, therefore considered appropriate to prepare dihydro derivative 7 related to 2 and study its neuromuscular blocking activity. Oxime of 3 β -hydroxy-5 α -androstan-17-one was reduced to 17 β -amine, which was methylated, and oxidized using





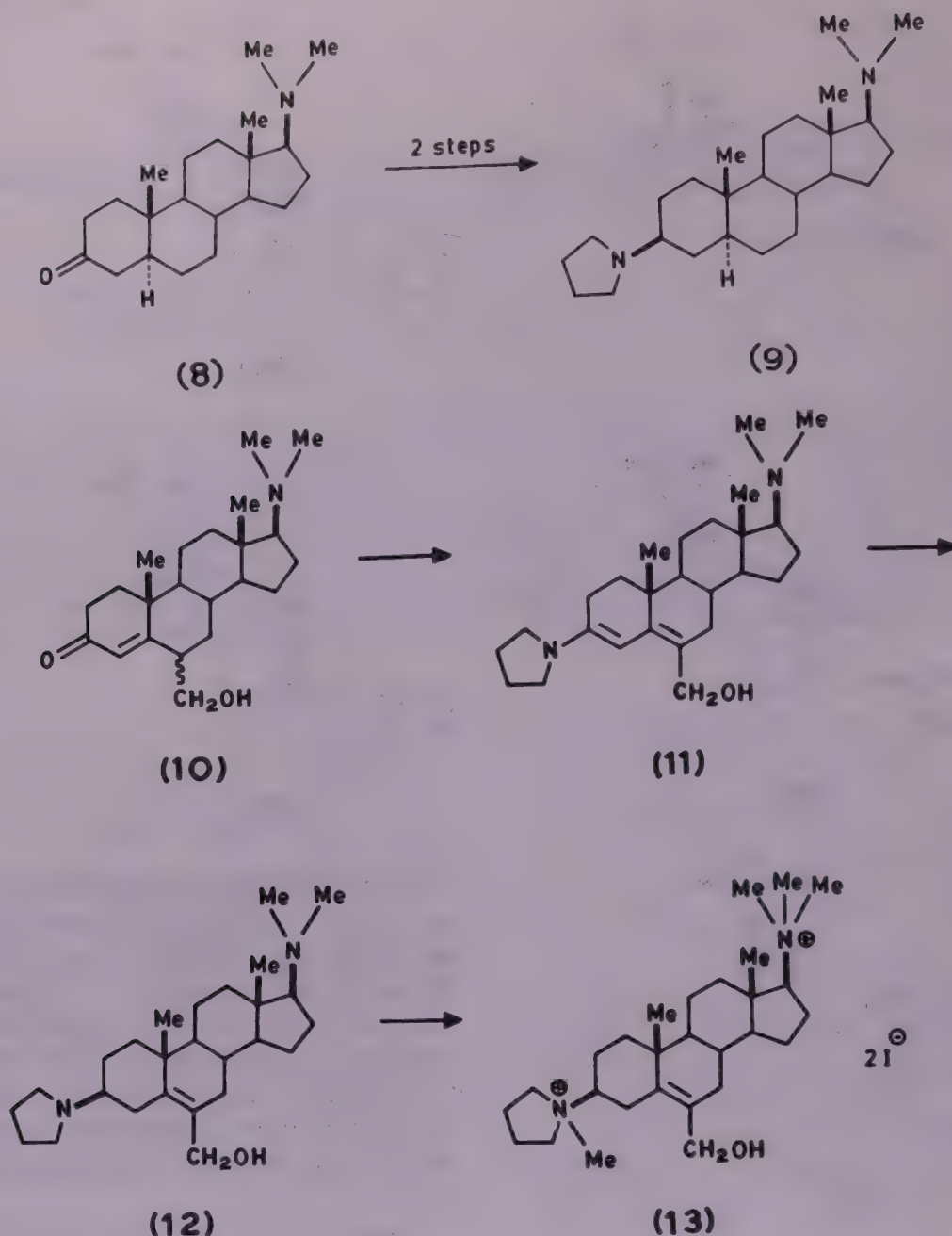
Jones' reagent to give the 3-one (8). The pyrrolidine-enamine of 8 on sodium borohydride reduction gave 9; the 3 β configuration being given on the basis of earlier reported reactions¹³. The methiodide 7 (HS-944) was prepared from 9.

Chandonium iodide (6) seems to have an appropriate hydrophilic to lipophilic ratio as a bisquaternary steroid system to exhibit potent nondepolarizing neuromuscular blocking activity. Similar ratios are apparent in the new bisquaternary compounds described above. To assess as to what extent and fashion the overall activities will be affected by changing hydrophilic-lipophilic balance, it was envisaged to prepare modifications having some other polar functions, say attached to ring-B.

In this context the work by Schneider *et al.*¹⁴ was found of interest. Following the procedure of Schneider *et al.* Accordingly, the dienamine 4 when treated

with formaldehyde in benzene-ethanol at room temperature gave hydroxymethyl derivative 10. The latter was further treated with pyrrolidine in benzene and the dienamine (11) obtained, on sodium borohydride reduction yielded a product which has been assigned structure (12) on the basis of its PMR spectrum. The compounds 10 and 12 are being examined through X-ray diffraction. The bisquaternary derivative (HS-892) 13 was obtained by treating 12 with methyl iodide.

The neuromuscular blocking activity of HS-854 (2), HS-1046 (dimethiodide of 6), HS-944 (7), and HS-892 (13), have been tested on rat phrenic nerve diaphragm preparation, using chandonium (1) as the standard. The IC₅₀ values have been calculated as 5, 30, 20, 20 and 20 μ g/ml for chandonium, HS-854, HS-1046, HS-944, and HS-892, respectively. It can be seen that none of the chemical modifications has led to a compound more potent than chandonium. The extra-nuclear placement of the quaternary head lowers the activity. Interestingly, HS-854 (2) is less active than the saturated relation HS-944 (7) and the 3 α -isomer (HS-1046) (dimethiodide of 6). It may be mentioned that 3 α -isomer (RGH-4201) (Duador) of dihydrochandonium is known to be equipotent with chandonium (1) in conscious dog though 2-3 times less active in anaesthetized cat¹⁵. The introduction of polar 6-hydroxymethyl function does not adversely affect the activity; in fact the analogue HS-892 (13) is more active than HS-854 (2). In the same test system the



19-nor-analogue HS-873 of HS-854 was shown to be somewhat more active (IC_{50} 25 $\mu\text{g/ml}$)⁶.

Experimental Procedure

The melting points reported are uncorrected. PMR spectra (90 MHz) were recorded in CDCl_3 with TMS as internal reference (chemical shifts in δ , ppm), IR spectra in KBr (ν_{max} in cm^{-1}), and UV spectra in methanol (λ_{max} in nm figures in parentheses refer to $\log \epsilon$ values). Purity of all the analytical samples was checked on silica gel G TLC plates, developed by exposure to iodine vapour. Anhydrous sodium sulphate was used as drying agent.

17 β -Amino-5-androsten-3 β -ol

Sodium metal (5.0 g) was added in small portions to a refluxing solution of 17-oximino-5-androsten-3 β -yl acetate¹⁶ (0.5 g) in 1-pentanol (100 ml). The reaction

mixture was refluxed till the sodium metal had reacted, cooled and steam-distilled to remove the solvent. The precipitated material was filtered, washed with water, dried and crystallised from pet ether (60–80°) to yield the product (0.35 g, 84.3%); m.p. 159–60° (lit.¹⁷ 155–60°); IR: 3240, 2810, and 1660; PMR: 0.65 (s, 3H), 1.02 (s, 3H), 2.67 (m, 1H), 3.45 (m, 1H) and 5.35 (m, 1H) (Found: C, 78.8; H, 11.2; N, 4.8. Calc. for $\text{C}_{19}\text{H}_{31}\text{NO}$: C, 78.8; H, 10.8; N, 4.8%).

17 β -Dimethylamino-5-androsten-3 β -ol

Sodium borohydride (0.25 g) was added in small portions during 0.5 hr to a stirred solution of 17 β -amino-5-androsten-3 β -ol (0.2 g) and formaldehyde (0.4 ml, 35%) in methanol (25 ml). The reaction mixture was poured into water (100 ml) and extracted with chloroform (4 $\times$ 25 ml). The extract was washed, dried and solvent removed under reduced pressure.

The residue on crystallisation from acetone gave the product (0.14 g, 66.5%); m.p. 208-10° (lit.⁸ 211-14-); IR: 3370, 2860 and 1600; PMR: 0.85 (s, 3H), 1.02 (s, 3H), 2.25 (s, 6H), 3.52 (m, 1H) and 5.35 (m, 1H) (Found: C, 79.4; H, 11.2; N, 4.5. Calc. for C₂₁H₃₅NO: C, 79.4; H, 11.1; N, 4.4%).

17β-Dimethylamino-4-androsten-3-one (3)

A solution of 17β-dimethylamino-5-androsten-3β-ol (2 g) and cyclohexanone (20 ml) in toluene (180 ml) was slowly distilled as aluminium isopropoxide (2 g) in toluene (10 ml) was added. Distillation was continued for 30 min till 40 ml of the distillate were collected. The mixture was refluxed for 3 hr and allowed to stand overnight. It was filtered, steam-distilled and the residue extracted with chloroform (4×50 ml). The combined chloroform extract was washed with water, dried and solvent removed. The residue was crystallised from acetone to yield 3 (1.1 g, 53%); m.p. 132-33° (lit.⁸ 131-34°); UV: 240 (4.22); IR: 3000, 1665 and 1615; PMR: 0.87 (s, 3H), 1.2 (s, 3H), 2.23 (s, 6H) and 5.74 (m, 1H) (Found: C, 79.8; H, 10.9; N, 4.4. Calc. for C₂₁H₃₃NO: C, 80.0; H, 10.5; N, 4.4%).

17β-Dimethylamino-3-pyrrolidino-3, 5-androsten (4)

Freshly distilled pyrrolidine (2.0 ml) was added to a boiling solution of 3⁸ (2.4 g) in methanol (40 ml). The reaction mixture was concentrated. The yellow needles which crystallised out on cooling were filtered, washed with methanol and dried to yield 4 (2.4 g, 85.0%); m.p. 171-72° UV: 278 (3.82); IR: 3000, 1640 and 1615; PMR: 0.85 (s, 3H), 1.0 (s, 3H), 2.21 (s, 6H), 3.12 (m, 4H) 4.8 (bs, 1H) and 5.05 (m, 1H) (Found: N, 7.6. Calc. for C₂₅H₄₀N₂: N, 7.6%).

17β-Dimethylamino-3β-pyrrolidino-5-androstene (5)

Sodium borohydride (1.0 g) was added to a stirred solution of 4 (1.0 g) in methanol (25 ml) during 4 hr. The reaction mixture was stirred for further 2 hr and poured into ice-cold water. The precipitated material was extracted with chloroform (3×25 ml) and processed. The residue was crystallised from acetone to yield 5 (0.6 g, 60.0%); m.p. 154-56°; IR: 2875, 2705 and 1665; PMR: 0.85 (s, 3H), 1.0 (s, 3H), 2.22 (s, 6H), 2.6 (m, 4H) and 5.35 (m, 1H) (Found: C, 80.4; H, 11.4; N, 7.5. Calc. for C₂₅H₄₂N₂: C, 81.0; H, 11.4; N, 7.6%).

17β-Dimethylamino-3α-pyrrolidino-5-androsten (6)

After separation of 5 by repeated crystallisations from acetone another compound 6 was got in pure form from the mother liquor, m.p. 171-73°; IR: 2860, 2700 and 1660; PMR: 0.86 (s, 3H), 1.05 (s, 3H), 2.30 (s, 6H), 2.57 (m, 4H) and 5.34 (m, 1H) (Found: C, 81.1; H, 11.1; N, 7.6. Calc. for C₂₅H₄₂N₂: C, 81.0; H, 11.4; N, 7.6%).

17β-Dimethylamino-3β-pyrrolidino-5-androstene dimethiodide (HS-854) (2)

Methyl iodide (0.2 ml) was added to a boiling solution of 5 (0.2 g) in absolute ethanol (0.5 ml). The mixture was refluxed for 1 hr, cooled and poured into dry solvent ether. The precipitated material was filtered and crystallised from methanol to yield HS-854 (2) (0.2 g, 57.0%); m.p. 336-38° (Found: C, 49.2; H, 7.4; N, 4.4. Calc. for C₂₇H₄₈I₂N₂: C, 49.5; H, 7.2; N, 4.3%).

17β-Dimethylamino-3β-pyrrolidino-5-androstene dimethiodide (HS-1046) (Dimethiodide of 6)

Bisquaternization of 6, as in the case of 2, yielded HS-1046 in 57% yield which crystallised from methanol m.p. 280-82° (Found: I, 39.0; N, 3.9. Calc. for C₂₇H₄₈I₂N₂: I, 39.0; N, 4.3%).

17β-Dimethylamino-5α-androstan-3-one (8)

Jones' reagent (0.3 ml) was added dropwise with stirring to the cold solution (10-15°) of 17β-dimethylamino-5α-androstan-3β-ol⁸ (0.1 g) in acetone (20 ml, distilled from potassium permanganate). Distilled water (1 ml) was added simultaneously to dissolve the precipitated material. Further Jones' reagent (0.2 ml) was added after 1 hr and stirring was continued for 2 hr. Reaction mixture was diluted with water (200 ml) and extracted with chloroform (3×25 ml). The chloroform extract was washed with water, dried and solvent removed under reduced pressure. The residue was crystallised from pet ether (60-80°) to give 8 (0.7 g, 72.0%); m.p. 180-82°; IR: 1690; PMR: 0.88 (s, 3H), 1.0 (s, 3H) and 2.25 (s, 6H) (Found: N, 4.5. Calc. for C₂₁H₃₅NO: N, 4.4%).

17β-Dimethylamino-3β-pyrrolidino-2-androstene (enamine of 8)

Freshly distilled pyrrolidine (0.5 ml) was added to a well shaken boiling solution of 8 (1 g) in methanol (20 ml). The crystalline material which separated out on concentrating and cooling was filtered, washed with methanol and dried to give the product (1.0 g, 84.0%); m.p. 154-55° (d) (Found: C, 80.7; H, 11.5; N, 7.0. Calc. for C₂₅H₄₂N₂: C, 81.0; H, 11.4; N, 7.6%).

17β-Dimethylamino-3β-pyrrolidino-5α-androstane (9)

Sodium borohydride (0.25 g) was added to a stirred suspension of enamine of 8 (0.1 g) in methanol (10 ml) during 0.5 hr. The mixture was stirred for another 1.5 hr and diluted with water. The precipitated material was extracted with chloroform (3×25 ml). The combined organic extract was processed and solvent removed under reduced pressure. The residue was crystallised from acetone to give 9 (0.6 g, 62.0%); m.p.

140-41°; (Found: C, 80.7; H, 11.8; N, 7.4. Calc. for $C_{25}H_{44}N_2$: C, 80.6; H, 11.9; N, 7.4%).

17 β -Dimethylamino-3 β -pyrrolidino-5 α -androstene dimethiodide (HS-944) (7)

Bisquaternization of **9**, as in the case of **2**, gave HS-944 (**7**) in 51% yield which crystallised from methanol-acetone, m.p. 340-42°; (Found: I, 38.4; N, 4.2. Calc. for $C_{27}H_{50}I_2N_2$: I, 38.7; N, 4.3%).

6 ξ -Hydroxymethyl-17 β -dimethylamino-4-androstene-3-one (10)

Formaldehyde solution (0.2 ml, 35%) was added to a solution of **4** (0.4 g) in dry benzene (10 ml) and absolute ethanol (30 ml) under nitrogen atmosphere during 30 min at room temperature with constant stirring. The solvent was removed under reduced pressure and the residue was crystallised from acetone to yield **10** (0.1 g, 27.0%); m.p. 191-94°; UV: 243 (4.23); IR: 3335, 2875, 1685 and 1615; PMR: 0.85 (s, 3H), 1.20 (s, 3H), 3.62 (m, 2H) and 5.8 (s, 1H) (Found: C, 76.5; H, 10.4; N, 3.9. Calc. for $C_{22}H_{35}NO_2$: C, 76.5; H, 10.2; N, 4.0%).

6-Hydroxymethyl-17 β -dimethylamino-3-pyrrolidino-3, 5-androstadiene (11)

A solution of **10** (0.1 g) in benzene (25 ml) and pyrrolidine (1.4 ml) was refluxed vigorously for 4 hr. The water of the reaction was removed by use of Bidwell-Sterling moisture trap. The solvent was removed and residue was dried in *vacuo* to yield **11** (0.1 g, 81.0%); m.p. 95-105°; UV: 294 (4.11).

6-Hydroxymethyl-17 β -dimethylamino-3 β -pyrrolidino-5-androstene (12)

The enamine (**11**) (0.1 g) was added to methanol (5 ml) which has been previously stirred with sodium borohydride (0.01 g). More of sodium borohydride (0.08 g) was added to the above stirred solution during 6 hr. The reaction mixture was stirred for further 2 hr and poured into water. The precipitated material was extracted with chloroform (4 $\times$ 25 ml). The combined organic layer was processed and solvent removed. The

residue was crystallised from acetone to give **12** (0.03 g, 33.0%); m.p. 230-32°; IR: 3190 and 1615; PMR: 0.81 (s, 3H), 1.0 (s, 3H), 2.24 (s, 6H), 2.62 (m, 4H) and 4.11 (m, 2H) (Found: C, 77.8; H, 11.0; N, 6.6. Calc. for $C_{26}H_{44}N_2O$: C, 77.9; H, 11.1; N, 7.0%).

6-Hydroxymethyl-17 β -dimethylamino-3 β -pyrrolidino-5-androstene dimethiodide (HS-892) (13)

Bisquaternization of **12**, as in the case of **2** yielded HS-892 in 56% yield which crystallised from methanol-acetone m.p. 275-77° (Found: C, 48.7; H, 7.8; N, 4.1. Calc. for $C_{28}H_{50}I_2N_2O$: C, 49.1; H, 7.4; N, 4.1%).

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Metal Hydride Catalysed Rearrangement of Bicyclic Carbinols: Formation of an Unexpected Lactone during an Attempted Oxy-Cope Rearrangement

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Treatment of the bicyclic carbinols **7** and **8** with KH in dry THF, at ambient temperature, gives unexpectedly the tricyclic lactones **10** and **9** respectively, instead of the expected anionic Oxy-Cope rearrangement. Ethynylation of the bicyclic ketone **5** gives directly the tricyclic lactone **11**, while **6**, on similar treatment affords the lactone **12** and ethynyl carbinol **13**.

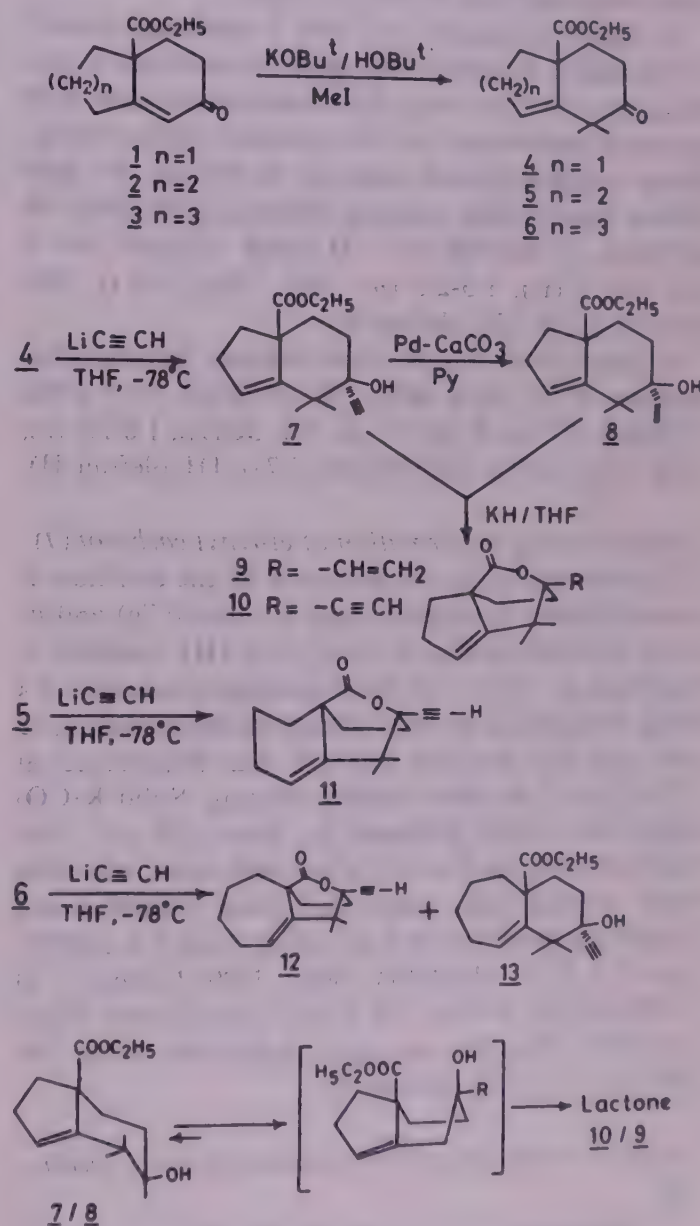
Oxy-Cope rearrangements leading to several naturally occurring molecules is well documented¹. Evan's discovery that the rate of the Oxy-Cope rearrangement was enhanced² upto a factor of 10^{17} by reaction of the anion of the allylic alcohol rather than the neutral compound, has greatly increased the usefulness of this process. In continuation^{3,4} of our studies on metal hydride promoted anionic Oxy-Cope rearrangement, we got interested in the synthesis and rearrangement of the bicyclic carbinols **7** and **8**.

Methylation of the bicyclic enone **1** (**2** and **3**) was carried out according to the procedure of Halsall *et al*⁵, in good yields. Ethynylation of bicyclic ketone **4** using lithium acetylide in THF at -78°C , gave the ethynyl carbinol (**7**) as a crystalline solid in 60% yield. Catalytic hydrogenation of **7** over Pd-CaCO₃ in pyridine at 30 psi led to the vinyl carbinol (**8**) in 85% yield. Treatment of (**8**) with KH in dry THF at ambient temperature, gave the tricyclic lactone **9** as a crystalline solid in 62% yield. Similarly **7** gave the corresponding lactone **10** in 56% yield.

The facile formation of lactone, instead of the Oxy-Cope rearrangement, indicated two important aspects of these ring systems: (i) the angular COOC₂H₅ and the tertiary OH groups are *cis* oriented (i.e. a, e) in the starting carbinol and (ii) the crossing over to the flexible form in which the COOC₂H₅ and OH groups occupy approximately axial positions (flag-pole-bowspirit) is seemingly a very facile process compared to the (3,3) sigmatropic rearrangements².

The latter aspect seems rather surprising since a molecular model of **7** showed the distinct possibility of encountering on Oxy-Cope rearrangement.

Ethynylation of the bicyclic ketone **5** using lithium acetylide under similar conditions, directly gave the lactone **11** in good yield (72%). However, in the case of bicyclic ketone **6**, ethynylation reaction produced both the lactone **12** and the ethynyl carbinol **13** in the ratio of 3:2.



Experimental Procedure

Boiling points and melting points are uncorrected. IR spectra were run on a Perkin-Elmer model 598 spectrophotometer, ¹H NMR on a Varian EM 390 90 MHz spectrophotometer and ¹³C NMR on a Jeol FX

90 Q (22.5 MHz) using TMS as internal standard. The IR, ^1H NMR and ^{13}C NMR of the new compounds were consistent with the assigned structures.

Ethyl 5,5-dimethylbicyclo [4.3.0] non-6-ene-4-one-1-carboxylate (4)

A solution of **1**⁷ (7.4 g, 0.035 mol) in *t*-butanol (30 ml) was added dropwise to a solution of potassium *t*-butoxide (from 5.5 g of potassium and 150 ml of *t*-butanol) at room temperature. After 15 min stirring, methyl iodide (15 g, 0.15 mol) was added, and the reaction mixture refluxed for 3 hr. The cooled solution was filtered, neutralized with 10% HCl and extracted with ether. Usual work-up of the ether extract gave **4** as a pale yellow liquid, b.p. 92-95°/0.5 mm in 80% yield (reported⁵ b.p. 92-96°/0.5 mm).

A similar treatment of **2** and **3** produced methyl 5,5-dimethyl bicyclo[4.4.0] dodec-6-ene-4-one-1-carboxylate (**5**) and ethyl 8,8-dimethylbicyclo[5.4.0] undec-6-ene-9-one-1-carboxylate(**6**) respectively. Their characterization data are as follows: **5** : pale yellow liquid (silica column; hexane), yield 55%; IR (CHCl₃) : 1720-1700 cm⁻¹; ^1H NMR (CCl₄): δ 1.0-1.1 (2s, 6H, CH₃), 1.5-2.5 (*m*, 10H, CH₂), 3.8 (*s*, 3H, OCH₃), 5.7 (*t*, 1H, olefinic H).

6: pale yellow liquid (silica column, hexane-ethyl acetate, 95:5), yield 40%; IR (CHCl₃): 1715-1705; ^1H NMR (CCl₄): δ 1.0-1.2 (3s, 9H, 3CH₃), 1.6-2.6 (*m*, 12H, CH₂), 3.9 (*q*, 2H, -OCH₂), 5.7 (*t*, 1H, olefinic H).

Ethynylation of 4: formation of ethynyl carbinol (7)

Lithium acetylide was prepared by the addition of *n*-butyllithium [prepared from lithium (0.7g) and *n*-butyl bromide (6.85g) in ether] to a THF solution of acetylene at -78°C. To this was added a solution of **4** (5.9g, 0.025 mol) in THF (25 ml) dropwise during 15 min and the reaction mixture was maintained at -78°C for 2 hr with constant stirring. Solid K₂CO₃ (10g) was added followed by water (20 ml). The reaction mixture was extracted with ether, the ether layer washed with water and dried (MgSO₄) and concentrated to furnish **7** as a solid, yield 3.6 g (60%), m.p. 121-22°C, IR (KBr) : 3640, 3300, 1720cm⁻¹; ^1H NMR (CCl₄) : δ 1.0 (*s*, 3H, CH₃), 1.1-1.3 (*t*, 6H, CH₃), 1.4-3.0 (*m*, 9H, CH₂, acetylenic H and OH), 4.2 (*q*, 2H, OCH₂), 5.7 (*s*, 1H, olefinic H).

Catalytic reduction of 7: formation of vinyl carbinol (8)

A solution of **7** (0.5 g) in dry pyridine (15 ml) was hydrogenated over Pd-CaCO₃ (40 mg) at 30 psi for 30 min. Pyridine was removed under reduced pressure, residual matter extracted with chloroform, the chloroform extract washed with 10% dil. HCl, water and dried. Removal of solvent gave **8**, yield 85% (0.42g),

m.p. 87-89°; IR (KBr): 3600, 1720, 1610cm⁻¹; ^1H NMR (CCl₄): δ 1.0 and 1.1 (2s, 6H, CH₃), 1.25 (*t*, 3H, CH₃), 1.4-2.8 (*m*, 9H, CH₂ and OH), 4.15 (*q*, 2H, OCH₂), 5.0-6.2 (*m*, 4H, vinyl protons and olefinic proton).

6,6-Dimethyl-8-oxa-7-vinyltricyclo[5.2.2.0^{1,5}] undec-4-ene-9-one (9)

Potassium hydride (0.25 g) was washed with dry hexane and taken up in dry THF. To this a solution of **8** (0.5 g) in THF (10 ml) was added dropwise, under nitrogen atmosphere, at room temperature. After 2 hr, the solvent was removed under reduced pressure and saturated NH₄Cl solution added and extracted with chloroform. The CHCl₃ extract was washed with water, dried and concentrated to furnish **9** as a solid, yield 62% (0.31g) m.p. 90-92°; IR(KBr) : 1760cm⁻¹; ^1H NMR (CCl₄) : δ 1.0 (*s*, 3H, CH₃), 1.2 (*s*, 3H, CH₃), 1.6-2.5 (*m*, 8H, CH₂), 5.1-6.0 (*m*, 4H vinyl and olefine protons); ^{13}C NMR (CDCl₃): δ 174.29, 149.44, 134.53, 120.49, 116.11, 87.88, 55.00, 31.32, 28.77, 27.8, 25.94, 24.77 and 24.61.

A similar treatment of **7** with potassium hydride produced the tricyclic lactone **10**, yield 62%; m.p. 140-42°; IR(KBr) : 3300, 1755cm⁻¹; ^1H NMR (CCl₄) : δ 1.2-1.3 (2s, 6H, 2CH₃), 1.7-2.6 (*m*, 8H, CH₂), 2.7 (*s*, 1H, acetylenic H), 5.6 (*t*, 1H, olefinic H).

7,7-Dimethyl-9-oxa-8-ethynyltricyclo [6.2.2.0^{1,6}] dodec-5-ene-10-one (11)

Ethynylation reaction of **5** (5.9 g, 0.025 mol) under the condition described for **4**, gave the lactone **11**, yield 73% (4.38g), m.p. 134-36°, IR(KBr) : 3300, 1755cm⁻¹; ^1H NMR (CCl₄) : δ 1.2 (*s*, 6H, 2CH₃), 1.4-2.2 (*m*, 10H, CH₂), 2.5 (*s*, 1H, acetylenic H), 5.5 (*t*, 1H, olefinic H).

Similar treatment of **6** (5.2 g, 0.02 mol) produced a mixture of 8,8-dimethyl-9-ethynyl-10-oxatricyclo [7.2.2.0^{1,7}] tridec-6-ene-11-one (**12**) and ethyl 5,5-dimethylbicyclo[5.4.0]undec-4-ethynyl-4-hydroxy-6-ene-1-carboxylate (**13**).

12: colourless needles from hexane, yield 35%, m.p. 139-41°, IR(KBr) : 3300, 1755; ^1H NMR (CCl₄) : δ 1.2 (*s*, 3H, CH₃), 1.29 (*s*, 3H, CH₃), 1.78 (*m*, 4H, CH₂), 2.18 (*m*, 8H, CH₂), 2.64 (*s*, 1H, acetylenic H), 6.01 (*t*, 1H, olefinic H); ^{13}C NMR (CDCl₃): 173.8, 147.9, 126.50, 82.36, 75.60, 48.68, 30.79, 29.3, 27.15, 26.44, 25.80, 23.70, and 20.78.

13 : pale yellow viscous liquid, yield 23%; IR(CHCl₃) 3560, 3300, 1720cm⁻¹; ^1H NMR (CDCl₃) : 1.2-1.35 (*t*, 9H, CH₃), 1.4-2.2 (*m*, 13H, CH₂), 2.7 (*s*, 1H, acetylenic H), 3.4 (*q*, 2H, OCH₂) 6.0 (*s*, 1H, olefinic H).

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Unusual Products of Catalytic Hydrogenation of 2, 2-Dimethyl-3-phenyl-4-(*p*-Hydroxyphenyl)-7-methoxychromene†

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Catalytic hydrogenation of 2, 2-dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychromene (**1**)¹ in THF over Pd-C at 1000 psi and 60-70° gives a mixture of *cis*-2, 2-dimethyl-3-phenyl-4-(4''-oxocyclohexyl)-7-methoxychroman (**3**) and *cis*-2, 2-dimethyl-3-phenyl-4-(4''-hydroxycyclohexyl)-7-methoxychroman (**4**) along with the major expected product *cis*-2, 2-dimethyl-3-phenyl-4-(4''-hydroxyphenyl)-7-methoxychroman (**2**, ~ 80%). Under similar conditions use of methanol as a cosolvent leads to the formation of *cis*-2, 2-dimethyl-3-phenyl-4-(4''-methoxycyclohexyl)-7-methoxychroman (**5**, 20%), in addition to a mixture of **3** and **4**. A probable reaction mechanism for this unexpected reduction of the phenyl ring in Pd-C catalysed reduction is proposed. Elaboration of 4-oxo function of **3** by reaction with lithium acetylide-ethylenediamine complex, ethyl magnesium bromide and *p*-benzyloxyphenylmagnesium bromide leads to isomeric mixtures of *cis*-2, 2-dimethyl-3-phenyl-4-(4''-hydroxy-4''-substitutedcyclohexyl)-7-methoxychroman derivatives. Stereochemical assignments have been made on the basis of ¹³CNMR studies.

Catalytic reduction of 2, 2-dimethyl-3-phenyl-4-*p*-hydroxyphenylchromene¹ (**1**) to the corresponding 3, 4-*cis*-chroman in large batches (~ 100 g) required as a drug intermediate, often led to the formation of a mixture of products significantly affecting the yield and purity of the required product. Present study was therefore, undertaken to characterize the byproducts formed and their further exploitation.

Thus, catalytic hydrogenation of **1** in THF over 10% + 5% (50% wet) Pd/C at 1000 psi and 60-70° led to a mixture of *cis*-2, 2-dimethyl-3-phenyl-4-(4''-hydroxycyclohexyl)-7-methoxychroman (**4**) and *cis*-2, 2-dimethyl-3-phenyl-4-(4''-oxocyclohexyl)-7-methoxychroman (**3**) in 10% yield along with the desired *cis*-2, 2-dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman¹ (**2**) (~80%). The above catalytic reduction of **1** in THF containing methanol led to partial formation of **5**.

Compounds **3** and **4** could not be separated because of very small difference in their *R_f* values in different solvent systems. The 3, 4-*cis*-geometry of **3** and **4** was assigned on the basis of the PMR spectrum of the mixture and comparison with that of **2**. The mixture of **3** and **4** on Jones' oxidation or sodium borohydride reduction led, respectively to exclusive formation of **4** and **3**. Use of methanol as cosolvent led to a partial formation of *cis*-2, 2-dimethyl-3-phenyl-4-(4''-methoxycyclohexyl)-7-methoxychroman (**5**).

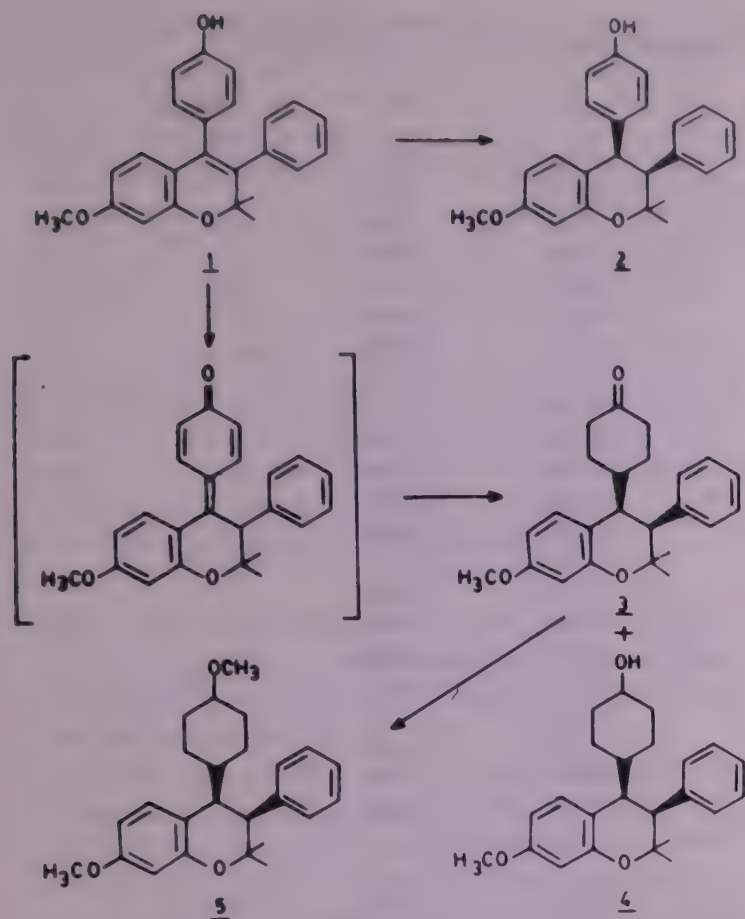
Treatment of **5** with BuLi in DMSO led to an

equilibrium mixture of **3**, 4-*cis* and *trans* products, instead of complete isomerisation as observed with **2**, wherein the abstraction of the relatively facile dibenzyllic proton at C-4 governed the stereochemical outcome.

This unusual reduction of aromatic ring during catalytic hydrogenation of **1** could be explained by a mechanism shown in Scheme 1. A relatively facile reduction of the nonaromatic quinonoid tautomer **2** which would sit on the catalyst on its least hindered side, would lead to the formation of 3, 4-*cis*-chroman. However, formation of these cyclohexyl compounds and their yields were neither consistent nor predictable. Formation of the 4-methoxy compound **5** is likely through hemiacetal, as reduction of **3** in methanol-THF in the presence of traces of acid led to the formation of **5** and **4**. Under similar condition in the presence of acid, **4** remained unchanged. However, **3** was recovered unchanged in the absence of acid. The inconsistent formation of **3**, **4** and **5** could be due to the presence of residual acid traces in the work-up of the Grignard reaction during the preparation of chromene **1** in some of the large batches.

Reaction of **3** with lithiumacetylide-ethylenediamine complex or ethylmagnesium bromide, led to isomeric mixtures of *cis*-2, 2-dimethyl-3-phenyl-4-(4α/4β-substituted-4α/4β-hydroxycyclohexyl)-7-methoxychromans (**6-9**) (Scheme 2). Isomers could be separated on preparative TLC.

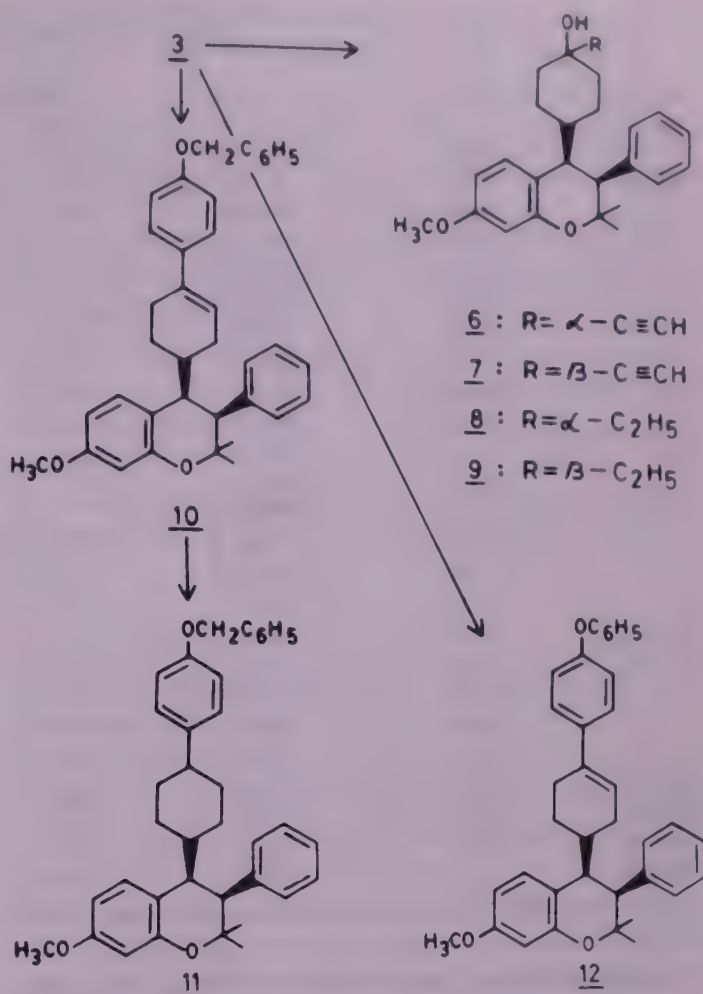
However, Grignard reaction with *p*-benzyloxyphenylmagnesium bromide on usual work-up gave the



Scheme 1

dehydrated product 3, 4-*cis*-2, 2-dimethyl-3-phenyl-4-[4-(4-benzyloxyphenyl) cyclohex-3-en-1-yl]-7-methoxychroman (**10**). All attempts to carry out debenzoylation of **10** were unsuccessful. Even hydrogenation under catalytic conditions, led to 3, 4-*cis*-2, 2-dimethyl-3-phenyl-4-[4-(4-benzyloxy phenyl) cyclohexyl]-7-methoxychroman (**11**) as shown by its mass spectrum (m/z 532). When the Grignard reaction was performed using 4-trimethylsilyloxyphenylmagnesium bromide, 3, 4-*cis*-2, 2-dimethyl-3-phenyl-[4-(4-(4-hydroxyphenoxy) phenyl)cyclohex-3-ene-1-yl]-7-methoxychroman (**12**) was obtained. Stereochemistry of the hydroxyl group at 4-position of the cyclohexyl ring in **6-9** was assigned on the basis of ^{13}C NMR.

In a substituted cyclohexanol, it is known² that a bulky substituent at C-4 prefers an equatorial orientation. Accordingly, in **6-9** the bulky chroman substituent is likely to be equatorial. Further, in such substituted cyclohexanols, the C-O bond of an axial hydroxyl is *gauche* with respect to C₂-C₃ (C₅-C₆) bond and *anti* in equatorial conformers. The non-bonded interactions between the axial oxygen and the axial hydrogens at C-3 and C-5 perturb the electron distribution causing shielding of the carbinyl carbon² by 5 ppm. Thus, in the present case, compounds **6** and **8** in which the C-4" quaternary carbon carrying the hydroxyl substituent appeared respectively at 65.95 and 70.99 ppm, were assigned axial (β) OH geometry and



Scheme 2

their counterparts **7** and **9** with C-4" appearing at 69.3 and 77.40 ppm respectively were assigned equatorial (α) OH conformation. Carbon-13 chemical shifts of **6-9** are given in Table 1.

Experimental Procedure

Melting points were taken in a sulphuric acid bath and are uncorrected. IR spectra were taken in KBr on Perkin-Elmer 157 and 133 spectrophotometers (ν_{max} in cm^{-1}), PMR spectra in CDCl_3 (chemical shifts in δ , ppm) on Perkin-Elmer R-32 (90 MHz) and EM-360 (60 MHz) NMR spectrometers using TMS as an internal reference. Carbon-13 NMR spectra were determined on a Bruker WM-400 spectrometer and mass spectra on JEOL-JMS D300 instrument.

Catalytic hydrogenation of 2,2-dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychromene (**1**)

A mixture of **1** (100 g), Pd-C [10%, 10 g and 5%, 50g, 50% wet] in THF (200 ml) and methanol (50 ml) was hydrogenated in an autoclave at 1000 psi pressure and elevated temperature (70-80°) for 4 hr. The catalyst was filtered, filtrate concentrated and the residual oil chromatographed through silica gel. Elution with solvent systems containing increasing proportion of

Table 1 — Carbon-13 Chemical Shifts of 6-9

Carbon No.	6	7	Multiplicity	8	9	Multiplicity
2	77.40	77.38	<i>s</i>	77.28	77.31	<i>s</i>
2-CH ₃	27.37	27.56	<i>q</i>	27.57	27.51	<i>q</i>
2-CH ₃	28.08	28.04	<i>q</i>	27.99	27.59	<i>q</i>
3	39.75	39.25	<i>s</i>	39.65	39.50	<i>s</i>
4	49.06	48.88	<i>d</i>	48.70	48.70	<i>d</i>
4a	115.03	115.19	<i>s</i>	115.12	115.16	<i>s</i>
5	130.43	130.52	<i>s</i>	130.37	130.43	<i>s</i>
6	107.39	107.39	<i>d</i>	107.29	107.41	<i>d</i>
7	159.22	159.33	<i>s</i>	159.27	159.15	<i>s</i>
8	102.38	102.33	<i>d</i>	102.20	102.20	<i>d</i>
8a	155.55	155.78	<i>s</i>	155.42	155.40	<i>s</i>
1'	140.67	140.57	<i>s</i>	140.91	140.89	<i>s</i>
2', 6'	127.72	127.65]		126.74]	126.68	
3', 4'	127.95	127.95]	<i>d</i>	127.67]	127.70	<i>d</i>
5'	126.76	126.28]		127.87]	127.90	
1''	39.75	38.63	<i>d</i>	38.68	38.58	<i>d</i>
2'', 3''	22.38	24.73]		23.55	22.25	
5'', 6''	25.59	27.74]	<i>t</i>	25.33]	25.85	<i>t</i>
	38.38	40.63		37.19]	36.38	
	39.29	40.75]		37.19]	36.38	
4''	65.95	69.30	<i>s</i>	70.90	77.40	<i>s</i>
OCH ₃	55.21	55.20	<i>q</i>	55.09	55.18	<i>q</i>
HC≡C	88.98	86.90	<i>s</i>			
-C≡CH	69.98	72.96	<i>d</i>			
4''-CH ₃				7.31	6.49	<i>q</i>

benzene in hexane gave a mixture of 3 and 4 in 10% yield and 5 in 30%.

cis-2, 2-Dimethyl-3-phenyl-4-(4''-oxocyclohexyl)-7-methoxychroman (3)

To a stirred solution of 3+4 (0.35 g, 0.009 mol) in acetone (KMnO₄-treated, 60 ml) under N₂ atmosphere at 0-5°, Jones' reagent (0.3 ml) was added and solution further stirred for 10 min. Reaction mixture poured into water, extracted with ethyl acetate, washed with water, dried (Na₂SO₄), concentrated to give an oil which on crystallisation from benzene-hexane gave colourless crystals of 3 (0.25 g, 73.5%), m.p. 178°; IR (KBr): 1720 (C=O), 1620, 1500 aromatic; PMR (CDCl₃): 1.0 and 1.45 (2*s*, 6H, 2×CH₃ *gem*-dimethyl), 3.8 (*s*, 3H, OCH₃), 6.4-7.3 (*m*, 8H, aromatic); MS: *m/z* 364 (M⁺) (Found: C, 78.8; H, 7.7. C₂₄H₂₈O₃ requires C, 79.1; H, 7.7%).

cis-2, 2-Dimethyl-3-phenyl-4-(4''-hydroxycyclohexyl)-7-methoxychroman (4)

To a stirred solution of 3+4 (1g) in ethanol (25 ml), sodium borohydride (1 g) was added and further stirred for 3 hr. Ethanol was removed, water added, extracted with ethyl acetate, washed with water, dried (Na₂SO₄) and concentrated to give an oil which was purified by column chromatography over silica gel to give 4, yield (0.8 g, 80%), m.p. 122°; IR(KBr): 3500

(OH), 3000 (CH₂), 1600, 1505 (aromatic); PMR (CDCl₃): 1.0 and 1.45 (2*s*, 6H, 2×CH₃, *gem*-dimethyl), 2.75 (*d*, 1H, 3-CH), 3.8 (*s*, 3H, OCH₃), 6.4-7.2 (*m*, 8H, ArH); MS: *m/z* 366 (M⁺) (Found: C, 81.5; H, 8.0. C₂₄H₃₀O₃ requires C, 81.4; H, 7.9%).

cis-2,2-Dimethyl-3-phenyl-4-(4''-methoxycyclohexyl)-7-methoxychroman (5)

Melting point 130°; IR(KBr): 2900 (CH₂) 1600 (aromatic); PMR(CCl₄): 0.9 and 1.3 (2*s*, 6H, 2×CH₃), 2.9 (*s*, 3H, OCH₃), 3.7 (*s*, 3H, OCH₃), 6.2-7.2 (*m*, 8H, ArH); MS: *m/z* 386 (M⁺) (Found: C, 79.2; H, 8.5. C₂₅H₃₂O₃ requires C, 78.9; H, 8.4%).

cis-2,2-Dimethyl-3-phenyl-4-(4'' α -ethynyl-4'' β -hydroxycyclohexyl)-7-methoxychroman (6) and *cis*-2,2-dimethyl-3-phenyl-4-(4'' β -ethynyl-4'' α -hydroxycyclohexyl)-7-methoxychroman (7)

To a stirred solution of ethylenediamine (240 ml) through which dry acetylene was passed, were added small pieces of lithium metal (1.5 g, 0.214 mol). After complete dissolution of lithium metal (1 hr) 3 (1 g, 0.0027 mol) dissolved in dry THF (50 ml) was added to the above solution and further stirred for 2 hr. The reaction mixture was decomposed with NH₄Cl, water added, extracted with ether, the organic extract washed with water, dried (Na₂SO₄) and concentrated to give an isomeric mixture of 6 and 7 (0.75 g, 81.5%) as

an oil. **6** and **7** were separated on silica gel PTLC in 5% ethyl acetate-benzene (double run). **6**, m.p. 156°; IR(KBr): 3400 (OH), 3000 (CH₂), 1600, 1500 (aromatic); PMR(CDCl₃): 0.9 and 1.37 (2s, 6H, 2×CH₃, *gem*-dimethyl), 1.0 and 2.0 (*m*, 9H, CH₂ and CH of cyclohexyl ring), 2.2 (*s*, 1H, C≡CH), 3.7 (*s*, 3H, OCH₃), 6.2-7.2 (*m*, 8H, ArH); MS: *m/z* 390 (M⁺) (Found: C, 79.6; H, 7.5. C₂₆H₃₀O₃ requires C, 80.0; H, 7.6%).

7, m.p. 130°; IR(KBr): 3000 (CH₂), 1625 (aromatic); PMR(CDCl₃): 0.95 and 1.38 (2s, 6H, 2×CH₃ *gem*-dimethyl), 1.0-2.0 (*m*, 9H, CH₂ and CH of cyclohexyl ring), 2.16 (*s*, 1H, C≡CH), 3.7 (*s*, 3H, OCH₃), 6.2-7.2 (*m*, 8H, ArH); MS: *m/z* 390 (M⁺) (Found: C, 79.5; H, 7.3. C₂₆H₃₀O₃ requires C, 80.0; H, 7.6%).

cis-2,2-Dimethyl-3-phenyl-4-(4''α-ethyl-4''β-hydroxycyclohexyl)-7-methoxychroman (**8**) and *cis*-2,2-dimethyl-3-phenyl-4-(4''β-ethyl-4''α-hydroxycyclohexyl)-7-methoxychroman (**9**)

To a stirred solution of ethylmagnesium bromide (0.0041 mol), **3** (0.3 g, 0.00082 mol) dissolved in dry THF (25 ml) was added dropwise and further stirred for 3 hr. The reaction mixture was decomposed with water, extracted with ether, washed with water, dried (Na₂SO₄) and concentrated to give an isomeric mixture of **8** and **9** (0.25 g, 83.3%), as an oil, the component being separated by careful PTLC (silica gel) in 5% EtOAc-benzene.

8, oil; IR(Neat): 3200 (OH), 3000 (CH₂), 1620, 1520 (aromatic); PMR(CDCl₃): 0.5-2.0 (*m*, 21H, 2×CH₃, 2×CH₂CH₃, CH₂ and CH of cyclohexyl ring), 3.7 (*s*, 3H, OCH₃), 6.2-7.2 (*m*, 8H, ArH); MS: *m/z* 394 (M⁺) (Found: C, 79.1; H, 8.6. C₂₆H₃₄O₃ requires C, 79.5; H, 8.3%).

9, oil; IR(Neat): 3500 (OH), 3000 (CH₂), 1630, 1600 (aromatic); PMR(CDCl₃): 0.98 and 1.35 (2s, 6H, 2×CH₃, *gem*-dimethyl), 0.6-1.5 (*m*, 11H, CH₂CH₃, CH₂ and CH of cyclohexyl ring), 3.75 (*s*, 3H, OCH₃), 6.2-7.2 (*m*, 8H, ArH); MS: *m/z* 394 (M⁺) (Found: C, 79.8; H, 8.5. C₂₆H₃₄O₃ requires: C, 79.5; H, 8.3%).

cis-2,2-Dimethyl-3-phenyl-4-[4''-(*p*-benzyloxyphenyl)cyclohex-3-en-1-yl]-7-methoxychroman (**10**)

To a stirred solution of *p*-benzyloxyphenylmagnesium bromide (0.025 mol) in dry ether, **3** (3.0 g, 0.0082 mol) dissolved in dry THF was added dropwise and further stirred at room temperature for 3 hr. The reaction mixture was decomposed with dil HCl, extracted with ether, washed with water, dried (Na₂SO₄) and concentrated to give an oil which on crystallisation from benzene-hexane gave colourless crystals of **10** (2 g, 69.4%), m.p. 181°; IR(KBr): 1620, 1500 (aromatic); PMR(CDCl₃): 1.0 and 1.45 (2s, 6H, 2×CH₃, *gem*-dimethyl), 3.75 (*s*, 3H, OCH₃), 4.95 (*s*, 2H, CH₂C₆H₅), 6.4-7.3 (*m*, 17H, ArH); MS: *m/z* 530 (M⁺) (Found: C, 82.0; H, 7.1. C₃₇H₄₈O₃ requires C, 83.7; H, 7.1%).

cis-2,2-Dimethyl-3-phenyl-4-[4''(4-*p*-hydroxyphenoxy)phenylcyclohex-3-en-1-yl]-7-methoxychroman (**12**)

To a stirred solution of trimethylsilyloxyphenylmagnesium bromide (0.00685 mol) in dry THF, **3** (0.5 g, 0.0013 mol) in dry THF (20 ml) was added dropwise under N₂ atmosphere. Reaction mixture was further stirred for 3 hr, decomposed with dil HCl, extracted with ethyl acetate, washed with water, dried (Na₂SO₄) and solvent distilled to give an oil which was purified by PTLC to afford **12** (0.1 g, 37.73%) as an oil; IR(Neat): 3500 (OH), 1620, 1600 (aromatic); PMR(CDCl₃): 0.9 and 1.4 (2s, 6H, 2×CH₃, *gem*-dimethyl), 1.5-2.7 (*m*, 7H, CH₂ and CH of cyclohexyl ring), 3.7 (*s*, 3H, OCH₃), 6.4-7.2 (*m*, 18H, ArH); MS: *m/z* 532 (M⁺) (Found: C, 81.5; H, 6.5. C₃₆H₃₆O₄ requires C, 81.3; H, 6.7%).

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Oxidation of Triterpenoids: Part VIII—Oxidation of Taraxerone with Selenium Dioxide in *t*-Butanol

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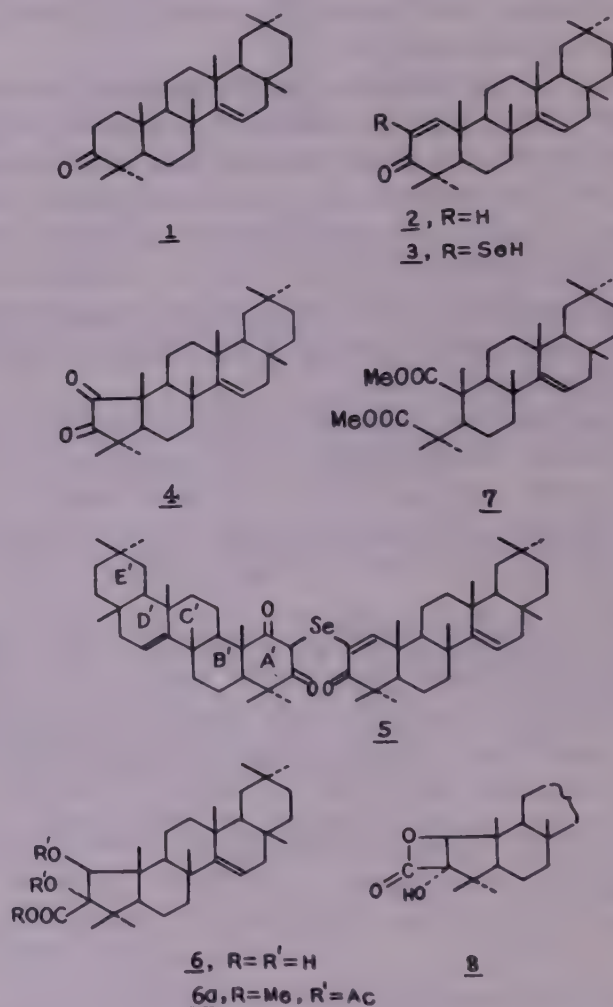
Taraxerone (1) on prolonged heating with selenium dioxide in *t*-butanol affords five products, viz 1(2)-dehydrotaraxerone (2), 1(2)-dehydrotaraxerone-2-selenide (3), 2-nor-taraxer-1, 3-dione (4) 1(2)-dehydrotaraxerone-2, 2'-seleno-taraxer-1', 3'-dione (5) and 1 β , 3 α -dihydroxy-3-carboxy-A-nor-taraxerone (6). The structures of these compounds have been established on the basis of analytical and spectral data.

In our earlier papers¹⁻⁶ we reported the formation of various products during the selenium dioxide oxidation in *t*-butanol of different triterpenoid ketones. Encouraged by the variety of products formed in these reactions we have presently studied the oxidation of taraxerone (1) by SeO₂. The carbonyl group of 1 sometimes behaves differently⁷ than the other 3-keto triterpenoids.

1 on oxidation with selenium dioxide in *t*-butanol formed five different compounds, A, B, C, D and E which were separated by chromatography and purified by crystallisation from CHCl₃-MeOH.

Compound A analysed for C₃₀H₄₆O (M⁺ 422) and was found to be identical with 1(2)-dehydrotaraxerone⁸ (2).

Compound B analysed for C₃₀H₄₅OSe (M⁺ 500) and had a carbonyl group with α , β -unsaturation and a trisubstituted double bond; its UV absorption at 302 nm was similar to that shown by lup-28-carbomethoxy-1(2)-en-3-one-2-selenide⁵ (3a). The mass spectrum displayed peaks at *m/z* 500 (M⁺), 421 (base), 311, 187, 161, 147, 133, 119, 105, 91, 77. Its PMR accounted for eight tertiary methyls appearing as singlets in the region δ 0.8 to 1.2 ppm, one olefinic proton at 5.57 (*dd*) typical of the C-15 proton of taraxerene skeleton and another olefinic proton, without neighbouring protons, at 7.16 ppm as a singlet. Carbon-13 NMR accounted for all the 30 carbons and the APT experiments⁹ indicated the existence of 8-CH₃ as a quartet, 8-CH₂ as a triplet, 5-CH as a doublet and 9-C- as a singlet; the singlet at δ 156.9 and doublet at 117.4 ppm were due to olefinic carbons at C-14 and C-15 typical of the taraxerene skeleton⁶; the doublet at δ 155.5 and singlet at 124.8 ppm were due to C-1 and C-2 olefinic carbon similar to those observed in 2a, and the C-3 carbonyl carbon appeared as a singlet at 202.4 ppm



about 15 ppm downfield than that of the parent ketone 1. On the basis of spectral data the compound has been assigned the structure as 1(2)-dehydro-taraxer-3-one-2-selenide (3).

Compound C analysed for C₃₀H₄₈O₃ (M⁺ 424) and had two carbonyl groups and a trisubstituted double bond as revealed by its IR spectrum. Its PMR spectrum exhibited signals in the region of δ 0.83 to

1.34 ppm as singlets for the eight tertiary methyls and C-15 olefinic proton at δ 5.5 ppm. The appearance of a three-proton singlet at δ 3.5 and a one-proton singlet at 3.1 ppm were rather difficult to explain. However, the PMR recorded elsewhere showed a shift of these two peaks by 0.5 ppm downfield with the other peaks appearing at the same positions. This was found to be due to methanol which must be present as methanol of crystallisation. Thus from mass, PMR spectrum and elemental analyses the molecular formula of the compound C was ascertained as $C_{29}H_{44}O_2 \cdot CH_3OH$. Its ^{13}C NMR spectrum accounted for only 29 carbons. The APT experiments showed the existence of $8-CH_3$ as a quartet, $8-CH_2$ as a triplet, $4-CH$ as a doublet and $9-C-$ as a singlet; the two singlets that appeared downfield at 212.4 and 203.0 ppm were due to two carbonyl carbons and the doublet at 117.4 and the singlet at 156.9 ppm were due to the C-14, 15 olefinic carbons. Assuming that the oxidation reaction has occurred only in ring-A of **1** with loss of either C-2 or C-3 carbon atom (on the basis of spectral data), compound C has been assigned the structure as 2-nor-taraxer-1, 3-dione (**4**).

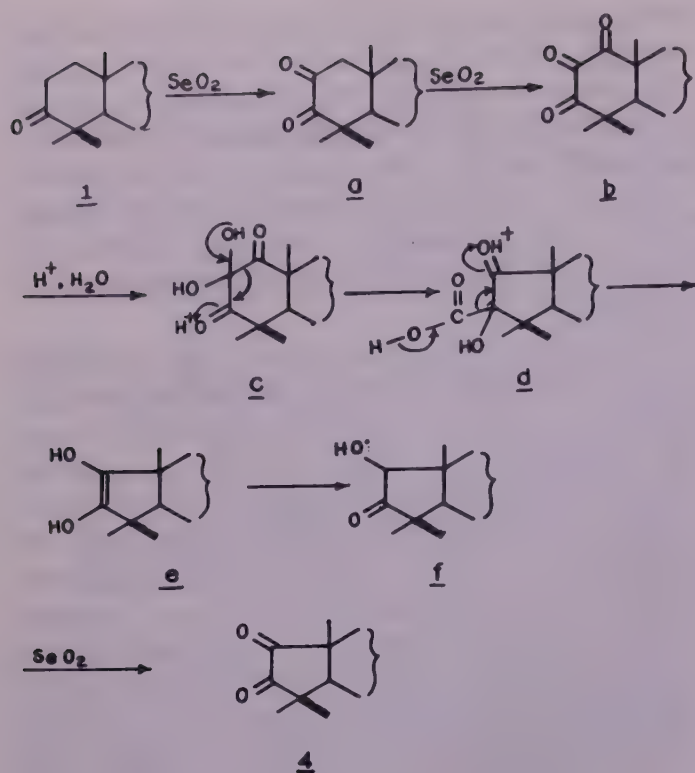
The structure **4** was further confirmed by hydrolysing compound C with methanolic KOH followed by esterification (with diazomethane) to obtain the ester which analysed for $C_{31}H_{50}O_4$ (M^+ 486). Its PMR displayed eight singlets in the region δ 0.82 to 1.25 for the eight tertiary methyls, two singlets for two carboxyl methyls at 3.64 and 3.65 and C-15 vinyl proton appeared at its usual position at 5.58 (*dd*). On the basis of spectral data the diester has been assigned the structure as methyl ester of 2-nor-seco-taraxer-1, 3-dicarboxylic acid (**7**).

Compound D analysed for $C_{60}H_{92}O_3Se$ (M^+ 938) has three carbonyl groups one of them being due to α , β -unsaturated carbonyl group as revealed by its IR spectrum. Its PMR spectrum was indicative of the presence of sixteen tertiary methyls in the region δ 0.83 to 1.3 ppm; a proton at 4.11 and a vinyl proton as a singlet at 7.3. The existence of a pair of double doublets in the region δ 5.5 to 5.6 for two protons clearly indicated that compound D contained two taraxerene skeletons in its molecule joined together by a selenium atom. The appearance of a single olefinic proton downfield at 7.3 is similar to that of **3** (compound B) indicating that one part of the molecule must contain structure similar to that of **3**. Its ^{13}C NMR accounted for sixty carbon atoms; the singlets downfield at 224.3, 205.0 and 200.7 ppm were due to three carbonyl carbons, the last one being carbonyl carbon with α , β -unsaturation; the doublet at 168.6 and singlet at 124.0 ppm could be due to olefinic carbons at C-1 and C-2 with selenium atom attached to C-2 carbon; the pair of singlets at 157.5 and 157.3

and a pair of doublet at 117.6 and 117.3 ppm were due to a pair of olefinic carbons at C-14 and C-15 of the two taraxerene moieties. The doublet carbon at 60.4 ppm coupled with the singlet protons at 4.11 ppm suggested that the carbon having a proton must be flanked by two carbonyl groups, itself being attached to the selenium atom. On the basis of the above spectral data the compound D has been assigned the structure **5**.

Compound E was most polar of the compounds isolated. It analysed for $C_{30}H_{48}O_4$ (M^+ 472) and has a carboxyl group and a hydroxyl group (s) as revealed by IR spectrum; its PMR spectrum accounted for eight tertiary methyls in the region δ 0.8 to 1.2 ppm. A one-proton singlet at 4.07 ppm indicated that this proton was an isolated one that was joined to a carbon containing an oxygen function. In order to establish the structure of the compound E, it was esterified with diazomethane and directly acetylated with Ac_2O -Py. The product F so obtained analysed for $C_{35}H_{54}O_6$ (M^+ 570). Its IR spectrum exhibited peaks at 1740 and 1240 cm^{-1} probably due to the methoxy ester and the acetate carbonyl groups. Its PMR exhibited sharp singlets in the region δ 0.82 to 1.2 ppm suggesting the presence of eight tertiary methyls, a three-proton singlet at 3.69 due to a carbomethoxy group, two three-proton singlets at 1.97 and 2.07 due to two acetoxy methyls and a one-proton singlet at 5.87. The singlet at δ 5.87 indicated that one of the acetoxy oxygens is attached to a carbon having a proton without any neighbouring proton. Further the olefinic proton at C-15 appeared at its usual position at δ 5.6 (*dd*). The methoxyl carbonyl group must be attached to a tertiary carbon as the PMR spectrum did not exhibit any peak in the region δ 2.1 to 3 ppm. Assuming once again that the oxidation occurred only in the ring-A of **1** the above data could be explained very satisfactorily if ring-A was considered to be five-membered having one carbomethoxyl and two acetoxy groups. Thus compound-F could be designated as 1, 3-diacetoxy-3-carbomethoxy-A-nor-taraxerene (**6a**) and the corresponding hydroxyl derivative as **6**. Further since on acetylation with Ac_2O -Py no dehydration occurred, it may be inferred that the two hydroxyl groups are in *trans* disposition.

In our previous communication⁵ we reported the formation of β -lactone derivative (**8**) on similar oxidation of dimethyl betulonate with selenium dioxide in *t*-butanol. The formation of **6** supports our previous mechanism⁵ for the formation of **8**. In the present case also a β -lactone would be formed during the oxidation which undergoes hydrolysis affording the dihydroxy acid (**6**). The formation of **4** could be explained via the intermediates a to f as shown in Scheme 1.



SCHEME 1

Experimental Procedure

Melting points are uncorrected. Petroleum ether had the b.p. $60\text{--}80^\circ\text{C}$. PMR spectra (TMS as internal standard) and ^{13}C NMR spectra (off resonance, internal TMS) were recorded in CDCl_3 on Bruker WH-400 and Bruker WH-270 with DEPT program respectively. IR spectra were recorded in nujol in Beckman-20; UV spectra in methanol on Shimadzu UV-240 and mass spectra on a Varian Mat 711 instrument (70 eV); column chromatography was performed over silica gel. Solvents used were dried over sodium metal. ^{13}C NMR data of compounds 3-5 are given in Table 1.

Oxidation of taraxerone (1) with SeO_2 in *t*-BuOH: Isolation of compounds A, B, C, D and E

A mixture of taraxerone (2 g), SeO_2 (2 g) and *t*-BuOH (200 ml) was refluxed for 24 hr. The solvent was distilled off under reduced pressure, the residue extracted with ether, washed with water and dried (Na_2SO_4). The residue obtained after removal of ether was chromatographed over silica gel (60 g) column. Elution with solvent mixture of increasing polarity furnished the following compounds: A (petroleum); B (0.5 g; petroleum-benzene, 4:1); C (0.2 g; petroleum-benzene, 3:1); D (0.6 g; petroleum-benzene, 1:4); and E (0.2 g; benzene-ethyl acetate, 4:1).

Compound-A was crystallised from CHCl_3 -MeOH to afford white crystals, m.p. $248\text{--}49^\circ$; IR: $1670, 1600, 820\text{ cm}^{-1}$; UV: 228 nm (ϵ , 11,000) (Found: C, 85.2; H, 10.9. Calc. for $\text{C}_{30}\text{H}_{46}\text{O}$: C, 85.3; H, 11.0%).

Table 1—Carbon-13 NMR Data of Compounds 3, 4 and 5 (data bracketed for carbons of rings A'-E)

Carbon	3	4	5
1	155.5 <i>d</i>	203.0 <i>s</i>	157.3 <i>d</i> (219.8 <i>s</i>)
2	124.8 <i>s</i>	—	124.4 <i>d</i> (60.4 <i>d</i>)
3	202.4 <i>s</i>	212.4 <i>s</i>	205.0 (224.3 <i>s</i>)
4	45.6 <i>s</i>	49.6 <i>s</i>	45.7 (50.2 <i>s</i>)
5	53.8 <i>d</i>	52.7 <i>d</i>	53.3 (50.3 <i>d</i>)
6	19.4 <i>t</i>	17.0 <i>t</i>	19.4 (19.0 <i>t</i>)
7	33.3 <i>t</i>	33.2 <i>t</i>	33.3 (33.3 <i>t</i>)
8	39.4 <i>s</i>	40.1 <i>s</i>	39.6 (40.1 <i>s</i>)
9	48.7 <i>d</i>	49.0 <i>d</i>	49.1 (48.8 <i>d</i>)
10	37.6 <i>s</i>	37.8 <i>s</i>	37.6 (37.6 <i>s</i>)
11	17.7 <i>t</i>	17.9 <i>t</i>	17.6 (18.6 <i>t</i>)
12	33.0 <i>t</i>	33.1 <i>t</i>	33.1 (33.1 <i>t</i>)
13	43.6 <i>s</i>	41.7 <i>s</i>	43.5 (43.8 <i>s</i>)
14	156.9 <i>s</i>	156.9 <i>s</i>	157.5 (157.3 <i>s</i>)
15	117.4 <i>d</i>	117.7 <i>d</i>	117.6 (117.3 <i>d</i>)
16	37.6 <i>t</i>	37.7 <i>t</i>	37.7 (37.7 <i>t</i>)
17	35.8 <i>s</i>	35.7 <i>s</i>	36.8 (36.8 <i>s</i>)
18	44.5 <i>d</i>	41.8 <i>d</i>	45.9 (48.8 <i>d</i>)
19	40.0 <i>t</i>	40.0 <i>t</i>	39.5 (40.3 <i>t</i>)
20	28.7 <i>s</i>	28.8 <i>t</i>	28.8 (28.8 <i>s</i>)
21	35.1 <i>t</i>	35.1 <i>t</i>	35.7 (35.1 <i>t</i>)
22	36.5 <i>t</i>	36.7 <i>t</i>	36.7 (35.7 <i>t</i>)
23	27.6 <i>q</i>	29.9 <i>q</i>	27.5 (29.9 <i>q</i>)
24	21.7 <i>q</i>	21.8 <i>q</i>	21.4 (21.4 <i>q</i>)
25	21.9 <i>q</i>	26.0 <i>q</i>	21.3 (21.7 <i>q</i>)
26	17.7 <i>q</i>	12.2 <i>q</i>	17.6 (16.3 <i>q</i>)
27	29.9 <i>q</i>	29.9 <i>q</i>	29.9 (29.9 <i>q</i>)
28	27.6 <i>q</i>	26.8 <i>q</i>	27.6 (28.8 <i>q</i>)
29	33.4 <i>q</i>	33.4 <i>q</i>	33.3 (33.3 <i>q</i>)
30	19.2 <i>q</i>	21.2 <i>q</i>	21.8 (21.4 <i>q</i>)

Compound-B was crystallised from CHCl_3 -MeOH, m.p. $282\text{--}83^\circ$; IR: $1740, 1600, 820$; UV: 302 (ϵ , 300); MS: m/z 500, 421 (base), 377, 311, 297, 187, 161, 147, 133, 119, 105, 91, 77; PMR: 0.82, 0.86, 0.91, 0.97, 1.12, 1.15, 1.17, 1.19, (8*s*, 8-Me), 5.57 (*dd*, 1H, $>\text{C}=\text{CH}-$), 7.16 (*s*, 1H, $>\text{C}=\text{CH}-\text{Se}$) (Found: C, 71.9; H, 9.1. $\text{C}_{30}\text{H}_{45}\text{OSe}$ requires C, 72.0; H, 9.0%).

Compound-C was crystallised from CHCl_3 -MeOH, m.p. $260\text{--}61^\circ$; IR: $1670, 1680, 800\text{ cm}^{-1}$; UV: no absorption above 220 nm ; MS: m/z 424, 346 300, 285, 272, 259, 257, 229, 205, 204, 127 (base); PMR: 0.82, (*s*, 2-Me), 0.92, 0.9, 0.96, 0.99, 1.01, 1.07, 1.06 (*ss*, 6-Me), 3.11 (*s*, OMe), 3.57 (*s*, 1H, OH), 5.52 (*dd*, 1H, $>\text{C}=\text{CH}-$) (Found: C, 79.1; H, 10.3. $\text{C}_{30}\text{H}_{48}\text{O}_3$ requires C, 78.9; H, 10.6%).

Compound-D was crystallised from CHCl_3 -MeOH to afford lemon yellow crystalline solid, m.p. $300\text{--}02^\circ$; IR: $1710, 1695, 1680, 820\text{ cm}^{-1}$; UV: $220\text{--}235$ (hump) and $295\text{--}315$ (hump) nm; MS: m/z 938, 857, 733, 653, 502, 500, 438, 341, 207, 187, 133; PMR: 0.83; 0.84 (2-Me), 0.92 (2-Me), 0.95 (2-Me), 0.99, 1.08, 1.14, 1.15 (2-Me), 1.17, 1.28 (2-Me), 1.31 (total 16-Me), 4.11 (*s*, 1H, $-\text{CH}-\text{Se}-$), 5.55 (*dd*, 1H, $-\text{C}=\text{CH}-$), 5.57 (*dd*, 1H, $-\text{C}=\text{CH}-$), 7.3 (*s*, 1H, $-\text{CH}=\text{CSe}-\text{CO}-$) (Found: C, 76.6; H, 9.9. $\text{C}_{60}\text{H}_{92}\text{O}_3\text{Se}$ requires C, 76.8; H, 9.6%).

Compound-E was crystallised from CHCl_3 -MeOH, m.p. 275-76°; IR: 3300-2700 (*b*, OH and COOH), 1700 (COOH), 820 cm^{-1} ; UV: no absorption above 220 nm; MS: m/z 472, 454, 439, 438, 423, 395, 204, 189; PMR: δ 0.83, 0.91, 0.96 (2-Me), 0.99, 1.02, 1.13, 1.20, (8-Me), 4.07 (*s*, 1H, $-\dot{\text{C}}\text{H}-\text{OH}$) (Found: C, 76.0; H, 10.1. $\text{C}_{30}\text{H}_{48}\text{O}_4$ requires C, 76.2; H, 10.2%).

Hydrolysis of compound C: Preparation of 2-nor-taraxer-1, 3-dicarboxylic acid

Compound C (0.1 g) was refluxed with methanolic KOH (10%) for 4 hr. The reaction mixture was cooled after removal of the solvent under reduced pressure. It was acidified with dil HCl, kept at 5° for 4 hr and then filtered. The residue failed to crystallise from CHCl_3 -MeOH. The amorphous solid was treated with an ethereal soln of CH_2N_2 and the resulting ester crystallised from CHCl_3 -MeOH, m.p. 162-63°; IR: 1740, 820 cm^{-1} ; MS: 486, 472, 454, 426, 411, 385, 362, 302, 303, 287, 261, 281, 204 (base), 189, 121; PMR: 0.82, 0.89, 0.91, 0.96, 1.08, 1.13, 1.18, 1.25, (8*s*, 8-Me), 3.64 (2*s*, 2-COOMe), 5.58 (*dd*, 1H, $\text{C}=\text{CH}-$), (Found: C, 76.3; H, 10.3. $\text{C}_{31}\text{H}_{50}\text{O}_4$ requires C, 76.5; H, 10.4%).

Ester-acetate derivative of compound E

Compound E (0.1 g) dissolved in ether was treated with ethereal CH_2N_2 at 5°C and kept for 6 hr. The solution was washed with aq. AcOH followed by water till neutral. Ether was removed by distillation and the residue after drying was acetylated Py(2 ml)/Ac₂O(2 ml) and kept over a water-bath overnight. The mixture was cooled, poured into cooled water and filtered. The

residue was washed thoroughly with water, dried and chromatographed over silica gel column. Elution of the column with petroleum furnished compound F (0.05 g) that crystallised from CHCl_3 -MeOH, m.p. 262-63°; IR: 1740, 1240, 820 cm^{-1} ; UV: no absorption above 220 nm; MS: m/z 570 (M^+), 555, 538, 451, 435, 414, 311, 267, 251, 218, 204, 189, 147, 133, 107, 99 (base); PMR: 0.83, 0.90, 0.91, 0.92, 0.95, 1.1, 1.17, 1.18 (8*s*, 8-Me), 1.97 (*s*, 3H, OAc), 2.07 (*s*, 3H, OAc), 3.69 (*s*, 3H, -COOMe), 5.6 (*m*, 1H, $\text{C}=\text{CH}-$), 5.87 (*s*, 1H, $\text{CH}-\text{OAc}$) (Found: C, 72.9; H, 9.6. $\text{C}_{35}\text{H}_{54}\text{O}_6$ requires C, 73.1; H, 9.7%).

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Synthesis of 4-(2-Benzofuranyl)coumarins

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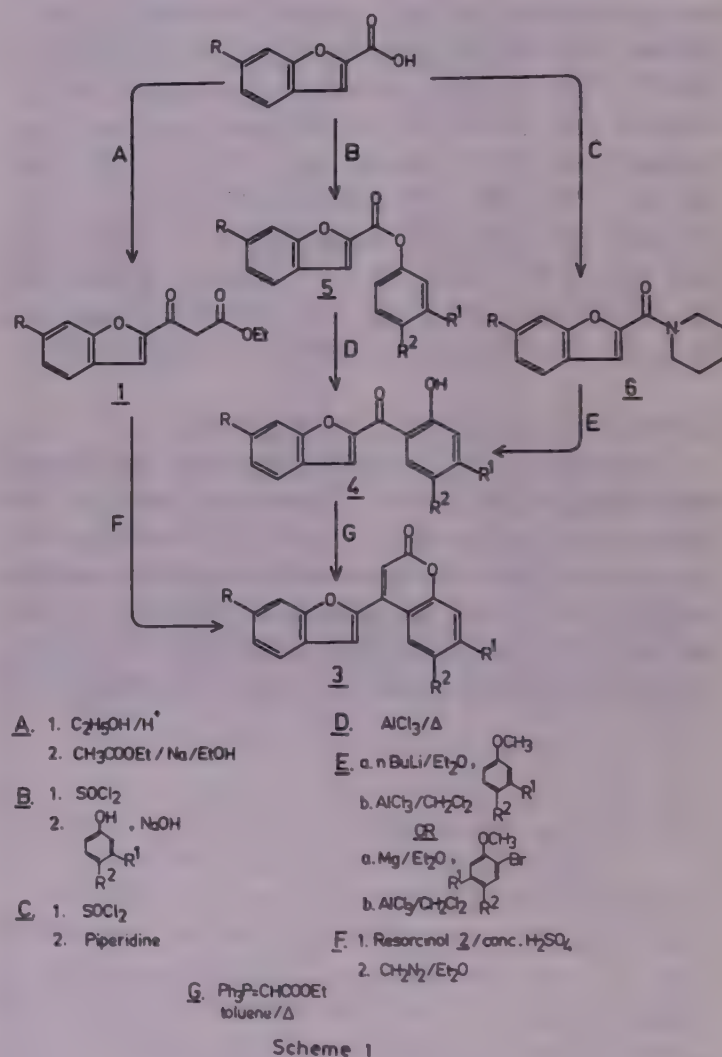
4-(2-Benzofuranyl)coumarins (**3**) have been synthesized by two routes, one involving Pechmann condensation of benzofuranpropionic acid- β -oxo-ethyl ester with phenols and the other involving Wittig reaction on 2-(2-hydroxybenzoyl)benzofuran using $\text{Ph}_3\text{P}=\text{CHCOOEt}$.

A recent report on the synthesis and pharmacological properties of the title compounds¹ prompt us to develop new routes for the synthesis of the above ring system. The reported synthesis¹ involves etherification of salicylaldehyde with 4-bromomethylcoumarins followed by base-catalysed condensation. Since 4-bromomethylcoumarins are light-sensitive² and are obtained in moderate yield^{3,6}, two alternative methods were explored for the synthesis of the title compounds. The first method involves construction of coumarin ring on the preformed benzofuran derivative using either Pechmann condensation or Wittig reaction.

The benzofuran derivative **1**, required for Pechmann reaction, was obtained by Claisen condensation of ethyl coumarilate with ethyl acetate. Although it failed to condense with phenol and cresols, it easily reacted with resorcinol (**2**) to give the corresponding hydroxy substituted benzofuranyl coumarin. It was then methylated with diazomethane to give 4-(2-benzofuranyl)-7-methoxycoumarin (**3a**) (68%) (Scheme 1). This approach is thus of limited application.

The second route involving Wittig reaction requires 2-(2-hydroxybenzoyl)benzofuran (**4**; $\text{R}=\text{R}^1=\text{R}^2=\text{H}$). It was prepared⁴ by Fries rearrangement of phenyl coumarilate (**5**) through lithiation of anisole and its reaction with coumarilamide⁷ (**6**) followed by demethylation¹ or through Grignard reaction of 2-bromoanisole with **6** followed by demethylation (Scheme 1). The last method gave **4** in a better yield.

The hydroxyketone (**4**) was then smoothly converted into **3b** ($\text{R}=\text{R}^1=\text{R}^2=\text{H}$) using $\text{Ph}_3\text{P}=\text{CHCOOEt}$ in dry toluene. Using the above strategy other substituted benzofuranyl coumarins (Table I) were also prepared. The intermediate ketones were either prepared through Fries rearrangement of the corresponding phenyl



coumarilate or through Friedel-Craft's acylation reaction (Scheme 1).

Thus, easy availability of the starting compounds, moderate reaction conditions and wider applicability make the latter route more convenient for preparing the title compounds.

Experimental Procedure

All melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 337 spectro-

*This compound is claimed to have been synthesized from 2-bromo-2'-hydroxyacetophenone and salicylaldehyde. In our recent communication⁴, we have shown that the reported reaction gives 2-(2-hydroxybenzylidene)coumaran-3-one instead of **4** and the melting point of **4b** is 64° and not 170° (ref. 9).

Table I—Melting Points and Yields of the Various Compounds Prepared

Compd	R	R ¹	R ²	m.p.* °C	Yield (%)
5b	H	H	H	101	94
5c	OCH ₃	H	H	120	65
4b	H	H	H	64 (170) ^y	77
4c	OCH ₃	H	H	110 (205) ^y	78
4d	H	H	CH ₃	60	68
4e	OCH ₃	OCH ₃	H	116	55
3a	H	OCH ₃	H	162 (147) ¹	68
3b	H	H	H	157 (162) ¹	73
3c	OCH ₃	H	H	166	87
3d	H	H	CH ₃	158 (155) ¹	60
3e	OCH ₃	OCH ₃	H	170	89

* Literature values are given in parentheses.

photometer ($\nu_{\max}$ in cm^{-1}), PMR Spectra in CDCl_3 on a 90 MHz Perkin-Elmer R-32 instrument using TMS as an internal standard (chemical shifts in δ , ppm) and mass on a Finnigan MAT 1020, automated GC/MS instrument at 70 eV.

2-Benzofuranpropionic acid- β -oxo-ethyl ester (1, $R=H$)

Ethyl coumarilate (3 g, 0.015 mol), sodium (0.4 g, 0.015 mol), dry ethanol (0.5 ml) and ethyl acetate (1.55 ml, 0.017 mol) were refluxed for 2 hr. Usual work-up gave **1** as a thick oil, yield 2.5 g (70%) (Found: C, 67.3; H, 5.5. $\text{C}_{13}\text{H}_{12}\text{O}_4$ requires C, 67.2; H, 5.2%); IR: 1740, 1690 ($\text{C}=\text{O}$); PMR: 13.1 (1H, s, $\text{C}=\text{C}-\text{OH}$, exchanged with D_2O), 7.8-7.2 (5H, m, Ar-H), 5.87 (1H, s, $=\text{CH}-$, exchangeable with D_2O), 4.7-4.0 (m, $-\text{O}-\text{CH}_2-\text{CH}_3$), 3.95 (2H, s, $-\text{CH}_2-$, exchangeable with D_2O), 1.6-1.1 (m, $-\text{O}-\text{CH}_2-\text{CH}_3$).

The PMR spectrum of the above compound showed a 80:20 mixture of keto-enol tautomers.

4-(2-Benzofuranyl)-7-methoxycoumarin (3a)

An intimate mixture of **1** (0.002 mol), resorcinol (0.002 mol) and sulphuric acid (2.5 ml, 98%) was left overnight, poured into cold water, filtered and recrystallised from hexane-ethyl acetate to give the hydroxy compound, yield 68%.

The hydroxy compound (0.2 g, 0.00071 mol), in ether, was added to the ethereal solution of diazomethane (prepared from 1g nitrosomethylurea and 40 ml of 50% aq. potassium hydroxide) and kept overnight. Etheral solution was washed with water, dried over anhyd. sodium sulphate and solvent removed to give **3a**, m.p. 162° (Lit.¹ m.p. 147°), yield 0.2 g (95%)

(Found: C, 73.8; H, 3.9. $\text{C}_{18}\text{H}_{12}\text{O}_4$ requires C, 74.0; H, 4.1%); IR: 1740, ($\text{C}=\text{O}$); PMR: 8.3 (1H, d, $J=9\text{Hz}$, coumarin 5-H), 7.8-6.9 (7H, m, Ar-H), 6.7 (1H, s, coumarin 3-H), 3.85 (3H, s, OCH_3); MS: m/z 292 (M^+ , 84%), 264 (100%).

2-(2-Hydroxybenzoyl)benzofuran (4b; $R=R^1=R^2=H$)

(a) Anisole (1.62 ml, 0.015 mol) was lithiated using *n*-butyllithium and the (3.5 g, 0.015 mol). Usual work-up followed by column chromatography gave **4** m.p. 64° (ref. 8), yield 2 g (55%).

(b) The reaction of 2-bromoanisole (3.3 g, 0.017 mol), in the presence of magnesium (0.5 g, 0.019 mol) in ether (50 ml), with coumarilamide⁷ (4 g, 0.015 mol) gave after usual work-up the ketone **4b**, yield 3.15 g (75%).

Phenyl coumarilates (5b and 5c): General procedure

A mixture of appropriate coumarilic acid (0.016 mol) and thionyl chloride (5 ml) was refluxed for 1 hr, excess thionyl chloride removed and a solution of appropriate phenol (0.016 mol) in sodium hydroxide (9 ml, 10%) added to it. The resulting mixture was shaken vigorously and the precipitated solid filtered, washed and dried. Crystallisation from hexane-ethyl acetate gave the corresponding phenyl coumarilate **5b** or **5c**.

5b: (Found: C, 75.5; H, 4.1. $\text{C}_{15}\text{H}_{10}\text{O}_3$ requires C, 75.6; H, 4.2%); IR: 1750 ($\text{C}=\text{O}$); PMR: 7.8-7.1 (m, Ar-H).

5c: (Found: C, 71.6; H, 4.4. $\text{C}_{16}\text{H}_{12}\text{O}_4$ requires C, 71.6; H, 4.5%); IR: 172 ($\text{C}=\text{O}$); PMR: 7.6-6.9 (9H, m, Ar-H), 3.88 (3H, s, $\text{Ac}-\text{OCH}_3$).

2-(2-Hydroxybenzoyl)benzofurans (4b and 4c): General procedure

An intimate mixture of anhyd. aluminium chloride (0.0075 mol) and appropriate phenyl coumarilate (0.004 mol) was heated in an oil-bath at 130-135° for 2 hr. Usual work-up gave a residue which on purification by column chromatography followed by crystallisation from aq. ethanol gave **4b** or **4c**.

4b: (Found: C, 75.4; H, 4.1. $\text{C}_{15}\text{H}_{10}\text{O}_3$ requires C, 75.6; H, 4.2%); IR: 1630 ($\text{C}=\text{O}$); PMR: 12 (1H, s, Ar-OH, exchangeable with D_2O), 8.4 (1H, dd, $J=9\text{Hz}$, 2Hz, benzoyl 6-H), 7.8-6.8 (8H, m, Ar-H).

4c: (Found: C, 71.5; H, 4.4. $\text{C}_{16}\text{H}_{12}\text{O}_4$ requires C, 71.6; H, 4.5%); PMR: 11.82 (1H, s, Ar-OH, exchangeable with D_2O), 8.16 (1H, dd, $J=9\text{Hz}$, 2Hz, aroyl 6-H), 7.45-6.6 (7H, m, Ar-H), 3.66 (3H, s, Ar- OCH_3).

2-(2-Hydroxyaroyl)benzofurans (4d and 4e): General procedure

Appropriate coumarilic acid (0.016 mol) and thionyl chloride (5 ml) were refluxed for 1 hr. Excess thionyl chloride was removed and the residue added to a well stirred suspension of anhyd. aluminium chloride (0.025 mol) in dry dichloromethane (20 ml). It was stirred for 30 min, appropriate methyl ether (0.013 mol) added and the mixture left overnight. Usual work-up and purification by column chromatography over silica-gel using benzene gave **4d** or **4e**.

4d: PMR: 7.8-6.5 (8H, *m*, Ar-H), 5.65 (1H, *bs*, Ar-OH, exchangeable with D₂O), 2.35 (3H, *s*, Ar-CH₃).

4e: (Found: C, 68.4; H, 4.6. C₁₇H₁₄O₅ requires C, 68.5; H, 4.7%); IR: 1670 (C=O); PMR: 12.85 (1H, *s*, Ar-OH, exchangeable with D₂O), 8.35 (1H, *d*, *J*=9Hz, aroyl 6-H), 7.7-7.5 (2H, *m*, benzofuran 3-H and 4-H), 7.1 (1H, *bs*, benzofuran 7-H), 6.99 (1H, *dd*, *J*=9Hz, 2Hz, aroyl 5-H), 6.6-6.5 (2H, *m*, aroyl 3-H and benzofuran 5-H), 3.92 (3H, *s*, Ar-OCH₃), 3.9 (3H, *s*, Ar-OCH₃).

4-(2-Benzofuranyl)coumarins (3b-e): General procedure

A mixture of **4(b-e)** (0.002 mol) and Wittig reagent (0.002 mol) in dry toluene (15 ml) was refluxed for 4 hr. The residue obtained after removal of solvent was purified and crystallised from hexane, ethyl acetate to give **3(b-e)**.

3b: (Found: C, 77.7; H, 3.9. C₁₇H₁₀O₃ requires C, 77.9; H, 3.8%); IR: 1730 (C=O); PMR: 8.17 (1H, *dd*, *J*=9Hz, 2Hz, coumarin 5-H), 7.8-7.2 (8H, *m*, Ar-H), 6.8 (1H, *s*, coumarin 3-H).

3c: (Found: C, 73.9; H, 4.2. C₁₈H₁₂O₄ requires C, 74.0; H, 4.1%); IR: 1740 (C=O); PMR: 8.18 (1H, *dd*, *J*=9Hz, 2Hz, coumarin 5-H), 7.6-7.2 (5H, *m*, Ar-H), 7.08 (1H, *d*, *J*=2Hz, benzofuran 7-H), 6.95 (1H, *dd*, *J*=9Hz, 2Hz, benzofuran 5-H), 6.8 (1H, *s*, coumarin 3-H), 3.9 (3H, *s*, Ar-OCH₃).

3d: (Found: C, 78.1; H, 4.4. C₁₈H₁₂O₃ requires C, 78.3; H, 4.4%); IR: 1740 (C=O); PMR: 7.92 (1H, *bs*, coumarin 5-H), 7.8-7.2 (7H, *m*, Ar-H), 6.9 (1H, *s*, coumarin 3-H), 2.45 (3H, *s*, Ar-H₃).

3e: (Found: C, 70.6; H, 4.7. C₁₉H₁₄O₅ requires C, 70.8; H, 4.4%); IR: 1740 (C=O); PMR: 8.15 (1H, *d*, *J*=9Hz, coumarin 5-H), 7.55 (1H, *d*, *J*=9Hz, benzofuran 4-H), 7.47 (1H, *bs*, benzofuran 3-H), 7.12-6.8 (4H, *m*, Ar-H), 6.58 (1H, *s*, coumarin 3-H), 3.93 (3H, *s*, Ar-OCH₃), 3.91 (3H, *s*, Ar-OCH₃).

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Use of Ferric Chloride in Carbohydrate Reactions : Part V^a-Acetolysis of Methyl Hexopyranosides Using Ferric Chloride in Acetic Anhydride

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Treatment of methyl α -D-glucopyranoside and galactopyranosides with acetic anhydride-ferric chloride reagent results in the acetolysis of the glycosides. Anomeric mixtures of the sugar peracetates in their pyranose and furanose forms and acyclic peracetates are obtained. The rate of acetolysis is retarded by the introduction of a tosyl function at position- 6.

Acetolysis of alkyl glycosides and polysaccharides with acetic anhydride-sulphuric acid has been used widely for determining the stability of glycosidic bonds¹. In an earlier report² we had shown (i) that $\text{Ac}_2\text{O}-\text{FeCl}_3$ reagent could be used to prepare α -peracetates of the carbohydrates, (ii) and action of this reagent on D-xylose and L-arabinose gave a mixture of cyclic and open chain peracetates and (iii) acetylation of methyl glycosides with this reagent gave, initially, the corresponding tetraacetates in good yield (~95-98%) but when the reaction was prolonged, acetolysis took place and acetates of the parent sugars were obtained. However, yields of the resulting α -peracetates were poor and a syrupy material remained after separation of the crystals of the α -peracetates. This report describes results of studies carried out to understand and explain the above observations.

Materials and Methods

Distilled acetic anhydride and reagent grade ferric chloride (BDH) were used. Sugars and their derivatives were powdered and dried under reduced pressure (8 hr) prior to use. Melting points are uncorrected. Evaporation were carried out at 45° under reduced pressure. GLC was performed on a Perkin-Elmer 39208 gas chromatograph (FID) equipped with a glass column (6' $\times$ 1/8" o.d.) packed with 3% ECNSS-M on Gas Chrom Q. Peak areas were measured with a planimeter. PMR spectra were recorded on a 60 MHz Perkin-Elmer R12-B instrument in CDCl_3 using TMS as an internal standard.

General procedure of acetolysis— Sugar or its derivative (1 g) was added to a stirred solution of anhydrous ferric chloride (80 mg) in acetic anhydride (6 ml) and kept at room temperature. After the sugar had gone into solution, the temperature was raised to the desired level. For reactions in the cold, the reagent was cooled to the required temperature and carbohydrate added in small quantities with stirring. After the required time of reaction, the mixture was poured into ice water. If a solid separated, it was filtered, washed, dried and recrystallized from 95% ethanol. If a syrup resulted, it was taken into chloroform, the chloroform layer was washed with aq. sodium hydrogen carbonate, followed by water, and then dried (Na_2SO_4) and evaporated.

Results and Discussion

Details of various products formed are given in Table 1. Melting points, specific rotations, and PMR data of the recrystallized products corresponded with those of the standard compounds. Complete acetylation of the carbohydrates was evident by the absence of hydroxyl absorption (around 3500 cm^{-1}) in the IR spectrum.

Acetolysis of methyl α -D-glucopyranoside and methyl α -D-galactopyranoside was carried out at 60° for 3 hr during which time the glycosidic methyl group was removed completely². GLC of the acetolysis product of methyl α -D-glucopyranoside showed four peaks. The major peak and the shoulder corresponded to α - and β -D-glucopyranose pentaacetates respectively whereas the other two peaks were due to the furanose pentaacetate and open chain heptaacetate respectively. The acetolyzed reaction product gave a GLC pattern similar to that of the product obtained on acetylation of D-xylose with $\text{Ac}_2\text{O}-\text{FeCl}_3$ (ref. 2). The presence of pyranose and open chain acetates was confirmed by the characteristic H-1 proton signals in the PMR spectrum of the reaction product. Thus, PMR

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^bForms a part of the thesis of the author

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signals were observed at δ 6.84 (*d*, $J_{1,2}=4.6$ Hz) due to H-1 of the acyclic heptaacetate (the *J* value matches with that of hexa-O-acetyl-aldehydo-D-xylose aldehydrol^{2,3}), 6.28 (*d*, $J_{1,2}=3.6$ Hz) due to anomeric proton of penta-O-acetyl- α -D-glucopyranose and 5.7 (*d*, $J_{1,2}=6.6$ Hz) due to anomeric proton of β -D-glucopyranose pentaacetate. The signals for the anomeric protons of furanose acetates were not properly resolved.

GLC analysis of the acetolysis product of methyl α -D-galactopyranoside showed five distinct peaks of which the two major components corresponded with standard α - and β -penta-O-acetyl-D-galactopyranose whereas the other three were due to the α - and β -furanose pentaacetates, and hepta-O-acetyl-aldehydo-D-galactose aldehydrol respectively. The PMR spectrum of the reaction product confirmed the presence of these components, except the furanoid derivatives, showing characteristic H-1 signals at δ 6.76 (*d*, $J_{1,2} = 6.67$ Hz) due to the anomeric proton of the acyclic acetate (*J*-value corresponded to that of the open chain *arabino*-hexaacetate), 6.35 (*d*, $J_{1,2} = 1.5$ Hz) due to anomeric proton of the α -pyranose pentaacetate and 5.7 (*d*, $J_{1,2} = 7.7$ Hz) due to H-1 of the β -pyranose pentaacetate. As in the case of glucose, signals due to anomeric protons of the furanose pentaacetates were not properly resolved to assign α - or β -configuration. Reacetylation of the mixture of acetates did not show any change in the composition of the reaction product as judged by GLC. (Table 1). This is in contrast to the observation made on the acetylation of D-xylose with $\text{Ac}_2\text{O}-\text{FeCl}_3$, where repeated acetylation led to increase in the proportion of acyclic form². It thus appears that stability of the ring

in the hexopyranose sugars is enhanced by the presence of a substituent at C-5.

These results along with the observations made in earlier investigations^{4,5} suggest that Ac^+ attacks both the methoxy oxygen and the ring oxygen. In the former case, the pyranose pentaacetate is formed through a half-chair intermediate whereas the latter pathway would give a mixture of open chain heptaacetate and furanose and pyranose pentaacetates (Scheme 1). Lichtenthaler and Bambach⁵ have explained the formation of furanose and pyranose acetates on acetolysis of methyl 4-acetamido-4-deoxyhexopyranosides by invoking an open chain intermediate but did not report the isolation of any acyclic peracetate.

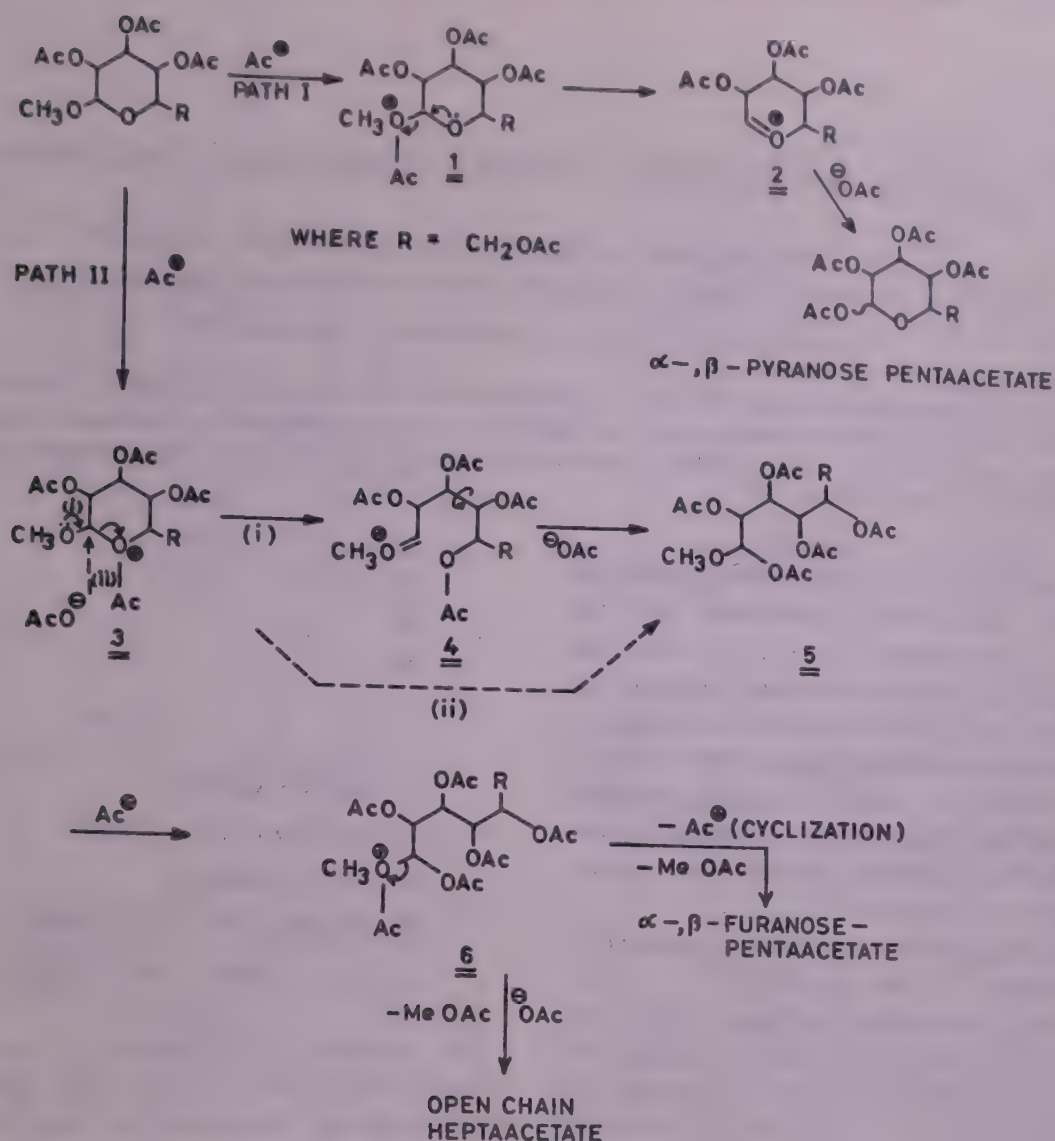
It is interesting to note that D-glucose on acetolysis for a prolonged period (70°/4 days) gave only a mixture of α - (major) and β -pyranose pentaacetates but no acyclic product was obtained. This indicates that there is no attack of Ac^+ on the ring oxygen. Thus, the presence of methoxyl group at C-1 must be increasing the nucleophilicity of the ring oxygen facilitating attack of Ac^+ on it and causing ring rupture. Hence, it may be concluded that the nature of the group or groups present at C-5 and /or C-1 will decide which of the two paths (I or II in Scheme 1) would predominate and also the rate as well as the number of products formed in acetolysis reactions.

Acetolysis of methyl 6-O-tosyl- α -D-glucopyranoside with $\text{Ac}_2\text{O}-\text{FeCl}_3$ was carried out at room temperature and at 60°, and the time required for the complete removal of methoxyl group was determined by monitoring the reaction by GLC and PMR measurement. Complete acetolysis to give 1,2,3,4-

Table 1 — Products Formed on Reaction of Methyl Glycosides with $\text{Ac}_2\text{O}-\text{FeCl}_3$

Carbohydrate	Reaction		Yield (%) of glycoside peracetate ^a	Products (% formed on acetolysis) ^{b,c}		
	Temp. °C	Time (min)		α -p- acetate	α -, β - acetates (p and f)	acyclic acetate
Me α -D-glucopyranoside	R.T.	10	98	-	-	-
	60	180	-	-	87.6	12.4
	reacetylation ^d	-	-	-	88.2	11.8
Me α -D-galactopyranoside	R.T.	7	90	-	-	-
	60	180	-	58.8	86.4	13.6
	reacetylation ^d	-	-	57.5	86.5	13.5
Me 6-O-tosyl- α -D-glucopyranoside	0-5	20	88 ^e	-	-	-
	60	720	-	82 ^{e,f}	-	-

(a) Recrystallized; (b) on the basis of peak areas measured by planimeter (areas measured by triangulation and using planimeter were identical upto the first decimal); (c) p = pyranose, f = furanose; (d) of the acetolysed product at 60° for 180 min; (e) Me 2, 3, 4-tri-O-acetyl-6-O-tosyl- α -D-glucopyranoside; and (f) 1, 2, 3, 4-tetra-O-acetyl-6-O-tosyl- α -D-glucopyranoside.



SCHEME 1

tetra-O-acetyl-6-O-tosyl- α -D-glucopyranose took place in 52-55 hr at room temperature and in 12 hr at 60° , showing a definite decrease in the reaction rate as compared to unsubstituted glycoside. The tosyl group at C-5 is expected to inhibit the formation of half-chair carbonium-oxonium ion (2, Scheme 1), since formation of 2 requires a small amount of rotation about C-2 and C-3, and C-4—C-5 bonds⁶. Presence of a bulky group at C-5 would thus adversely affect the rate of reaction. GLC of the reaction mixture showed a major single peak and the acetolyzed product could be easily crystallized to give the pure 6-O-tosyl- α -D-glucopyranose tetraacetate in good yield (80-90%). Absence of a complicated reaction product suggests that the reaction goes predominantly through path-I (Scheme 1). Furthermore, the tosyl group, in addition to producing a steric effect, reduces the nucleophilicity of the ring oxygen due to inductive (-I) effect, thereby retarding the attack of Ac^+ on it. Methyl 2,3,4-tri-O-

acetyl-6-O-tosyl- α -D-glucopyranoside was obtained in 60-65% yield by carrying out the reaction at 0.5° for 20-30 min, thereafter acetolysis of glycoside group commenced.

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Preparation & Cleavage of Some Cyclopropane Derivatives

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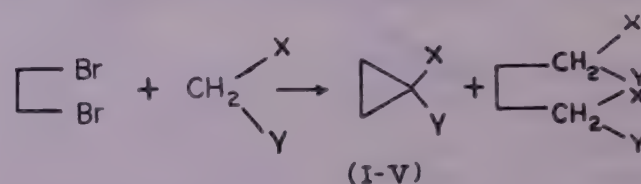
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Alkylation of active methylene compounds with 1, 2-dibromoethane using anhyd. K_2CO_3 /DMF at room temperature gives cyclopropane derivatives which undergo selective transformation by simple methods. Cyclopropanes, obtained by the condensation of α -diazoacetophenones with olefins, are cleaved to trisubstituted olefins with Grignard reagent. Hydration of the products has also been studied.

During the last three decades a number of methods and processes¹ have been developed for the preparation of cyclopropane and its derivatives. Among these, the methods which are employed for the preparation of cyclopropane derivatives are based on alkylation of acidic compounds using crown ethers^{2a}, quaternary ammonium salts^{2b-c}, phase transfer catalysis^{2f-h}, 1,2-dihaloalkanes with potassium carbonate in HMPA³ or dimethoxyethane⁴ and benzyl trimethyl ammonium hydroxide⁵.

In the present study cyclopropane derivatives (I-V) have been prepared by the alkylation of 1, 2-dibromoethane using potassium carbonate/DMF⁶ at room temperature. In these condensations reasonable reaction rates at room temperature were obtained only with compounds having pK_a of about 18. The reactions were carried out under stirring for 7 to 8 hr using excess (four times) of 1, 2-dibromoethane. The results are given in Table 1. Dibenzoyl methane did not give cyclopropane even on heating for 24 hr at 100° probably due to high stability (low nucleophilicity) of the anion.



I: $X=Y=-COOEt$

II: $X=-CN$; $Y=-COOEt$

III: $X=Y=-COCH_3$

IV: $X=C_6H_5CO-$; $Y=-COCH_3$

V: $X=-COOEt$; $Y=-COCH_3$

The cyclopropyl compounds (I-V) were treated separately with conc. H_2SO_4 , HBr (48%), isopropylamine and aq. ammonia. The acids at low temperature did not affect diethyl cyclopropane-1, 1-dicarboxylate (I) and ethyl 1-acetyl cyclopropane-1-carboxylate (V), while conc. sulphuric acid changed the cyano group of II to the amide group. Ammonolysis with aq. ammonia converted the ester group of I, II and V into the amide group. However, in the case of I only one of the two ester groups was converted into the amide function. The ester groups of I, II and V were hydrolysed on refluxing with 10% ethanolic KOH . The carbonyl function of one of the acetyl groups of III easily underwent reduction by Wolff-kishner and also with sodium borohydride giving 1-acetyl-1-ethylcyclopropane and 1-acetyl-1-(hydroxy ethyl) cyclopropane respectively.

Under the action of hydrobromic acid the cyclopropane rings of III and IV were cleaved producing the tri-substituted propanes. The cyclopropane rings of II-IV were also cleaved by refluxing with ethanolic isopropylamine for 5 hr giving IIa-IVa, respectively.

The reaction of α -diazoacetophenone with cyclohexene in the presence of copper salts gave 7-benzoylnorcaradiene (VIa). The cyclopropane ring can be cleaved or rearranged in various ways⁷. The cleavage of α -hydroxycyclopropane has been effected with 48%

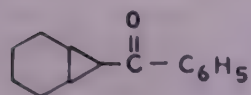
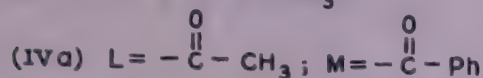
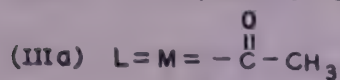
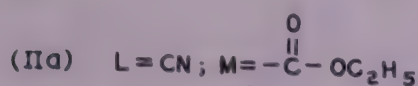
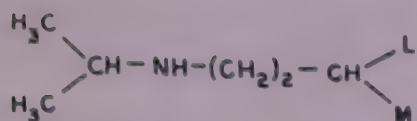
Table 1—Results of the Reaction of Active Methylene Compounds with Excess of 1, 2-Dibromoethane

Active methylene compound	Reaction temp. °C	Yield (%) of	
		Cyclopropane	1, 1, 4, 4-tetrasubstituted butane
Diethylmalonate	85-90	(I) 61	—
Ethylcyanoacetate	75-80	(II) 65	—
Acetylacetone	25	(III) 72	5
Benzoylacetone	50	(IV) 67	4
Ethylacetoacetate	80-90	(V) 63	—
Dibenzoylmethane	100	—	—

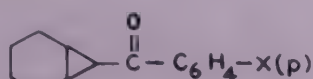
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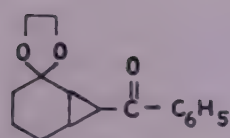


VIa

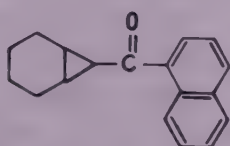


VIb x = Cl

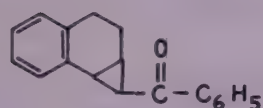
VIc x = OCH₃



VIc



VIe



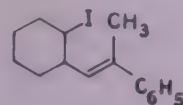
VIe

HBr⁸, magnesium^{8,9} and other halides⁹, mercuric acetate¹⁰ and other electron transfer processes¹¹ leading to homoallylic halide derivatives¹². The cyclopropane adducts (VIa-f), obtained from cyclohexene, cyclohexen-2-one or dihydronaphthalene by reaction with α -diazoacetophenones in the presence of active copper, were cleaved by reaction with Grignard reagents and subsequent dehydration gave olefins (VII, VIII, IX or X) which could be rehydrated (oxymercuration-demercuration)¹³.

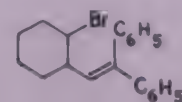
Oxymercuration with mercuric acetate in THF, followed by reduction in aq. sodium hydroxide with sodium borohydride was used for hydration.

Experimental Procedure

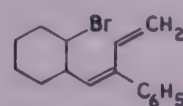
All melting and boiling points reported are uncorrected. Solvents and other starting materials were dried and purified before use. IR spectra recorded neat or in KBr on a Beckman IR-20 spectrometer (ν_{max} in cm^{-1}), PMR spectra were recorded at 60 MHz and 90 MHz on a Perkin-Elmer R-32 or Varian A-60 Instrument, using TMS as internal reference (chemical shifts in ppm), mass spectra on a Joel JMS-D 300 spectrophotometer, and UV-Vis spectra on Beckman



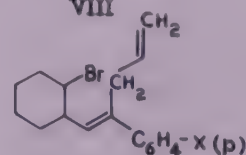
VII



VIII

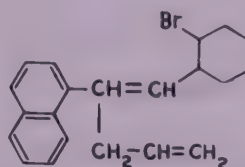


IX

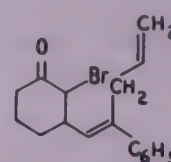


Xa x = Cl

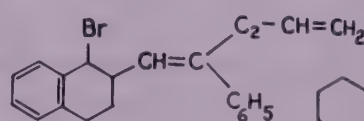
Xb x = OCH₃



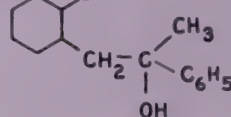
XI



XII



XIII



XIV

DU-2 and Shimadzu-UV-240 (Graphicord) spectrometers (λ_{max} in nm). Only the significant spectral data are given. Silica gel (E Merck) plates of 0.50-0.75 mm thickness were used for TLC studies. Silica gel (BDH) and alumina (SM) were employed for column chromatography.

Cyclopropane derivatives (Table 1): General Procedure

To a mixture of an active methylene compound (0.1 mol), anhyd. K_2CO_3 (0.24 mol) and DMF (125 ml) was added 1, 2-dibromoethane (0.4 mol) dropwise with stirring at room temperature during 1 hr. The stirring was continued further for 2 hr and then at a temperature as indicated in Table 1 for 2-3 hr. The reaction mixture was cooled, filtered and the residue washed with DMF (25 ml). The combined liquid was distilled at reduced pressure to a small amount which was treated with cold water and extracted with ether. The ether extract was washed with brine, dried and fractionated to give products as given in Table 1.

Diethyl cyclopropane-1, 1-dicarboxylate (I)

Yield 12.3g (60%), b.p. 90°-95°/10 mm; PMR¹⁴ (CDCl_3): 1.30 (t, $J=7\text{Hz}$, 6H, $2\times\text{CH}_3$); 1.50 (s, 4H, $-\text{CH}_2-\text{CH}_2-$), 4.40 (q, $J=7\text{Hz}$, 4H, $2\times\text{CH}_2$) Found: C, 57.9; H, 7.6. $\text{C}_9\text{H}_{14}\text{O}_4$ requires C, 58.1; H, 7.5%.

(a) *With ammonia*: The compound (0.030 mol) on treatment with aq. ammonia (10 ml, 28%) at room temperature for 3 hr gave a product which was identified as ethyl 1-carboxamidocyclopropane-1-carboxylate (3.5g, 74%), m.p. 124°-25° (lit.¹⁵ m.p. 124°) on the basis of elemental analysis and spectral data (IR, PMR, mass).

(b) *With alc. KOH*: On stirring I (0.1 mol) with KOH, 11.2g (0.2 mol) in ethanol (110 ml) overnight at room temperature followed by usual work up gave white needles (MeOH) of cyclopropane-1, 1-dicarboxylic acid (6.3g; m.p. 139°, lit. 140°), identical with an authentic sample prepared from sodiomalonic ester and ethylene dibromide.

Ethyl 1-cyano cyclopropane-1-carboxylate (II)

Yield 9g (64%), b.p. 80-85° / 10 mm: PMR (CDCl₃): 1.35(*t*, *J*=7Hz, 3H, CH₃), 1.50(*s*, 4H, -CH₂-CH₂), 4.40(*q*, *J*=7Hz, 2H, -CH₂), IR (neat): 3050(w), 2960(m), 2220(m), 1730(s), 1470-1450(m), 1310(s), 1270(w), 1210-1160(s), 1470-1450(m), 860(m), 740(m) (Found: C, 60.5; H, 6.5; N, 9.9. C₇H₉O₂N requires C, 60.4; H, 10.7; N, 10.1%).

(a) *With cold conc. H₂SO₄*: This compound (0.04 mol) on treatment with cold conc. H₂SO₄ 98% (5 ml) for 2 hr at -5° to -10° and then overnight in the cold gave a solid material which was washed with cold water till neutral to give ethyl 1-carboxamidocyclopropane-1-carboxylate (2.8g), 45% m.p. 124°-25°.

(b) *With ammonia*: Treatment of II (0.05 mol) with aq. ammonia (10 ml, 28%) overnight afforded, yield 4.2g (78%), m.p. 157° (Lit.¹⁵, m.p. 160°); elemental analysis and IR, PMR and mass spectral were compatible with its structure 1-cyanocyclopropane-1-carboxamide.

(c) *With alc. KOH*: Hydrolysis of II (0.05 mol) with 10% ethanolic KOH afforded 1-cyanocyclopropane-1-carboxylic acid (2.5g, 45%), m.p. 148° (Lit.¹⁶ m.p. 149°).

(d) *With isopropylamine*: Compound II (0.05 mol) was refluxed with dry isopropylamine (0.1 mol) for 5 hr on a water-bath ethanol (50 ml) removed, and the reaction mixture treated with cold water (50 ml) containing 10% acetic acid. Following products were isolated.

The liquid ethyl 2-cyano-4-(isopropylamino)butanoate (IIa) (5g, 50%), b.p. 135-140° / 5 mm; PMR (CDCl₃): 0.65-0.85(*t*, *J*=8Hz, 2H, C-3H), 1.0-1.25(*t*, *J*=7Hz, 6H, 2×CH₃), 1.4-1.6(*t*, *J*=7Hz, 3H, ester CH₃), 1.8-2(*t*, *J*=6 Hz, 2H, -CH₂), 2.2-2.6(*m*, *J*=6Hz, 2H, -CH₂), 2.9-3.0(*t*, *J*=7Hz, 1H, C-2H), 3.20-3.70(*m*, *J*=6Hz, 1H, -CH(CH₃)₂), 7.40(*s*, 1H, -NH-); MS: *m/z* (rel. intensity): 197(1), 151(20), 138(33), 123(52), 94(42), 66(32), 55(100), 54(80), 41(45), IR (neat): 3610-

3100(b,m), 2220(m), 1720-1690(s), 1460-1430(m), 1220(m) (Found: C, 60.1; H, 8.5; N, 14.1. C₁₀H₁₈N₂O₂ requires C, 60.6; H, 9.1; N, 14.2%).

The yellow solid, left in distilling flask, on chromatography over alumina column and elution with benzene-pet. ether (20:80) afford a white solid, 1-cyano-1-N-substituted amidocyclopropane (1.55g, 20%) m.p. 59-60°; PMR (CDCl₃): 1.05-1.30(*t*, *J*=8Hz, 6H, 2×CH₃), 1.50-1.60(*t*, *J*=4.5Hz, 2H, -CH₂-), 1.60-1.70(*t*, *J*=3.5Hz, 2H, -CH₂-), 3.15-3.50(*m*, *J*=7Hz, 1H, -CH(CH₃)₂), 6.30-6.90(*hump*, 1H, -NH-); MS: *m/z* (rel. int.): 152(1), 138(48), 123(67), 94(100), 66(45), 64(27), 44(33); IR (nujol): 3400-3300(b,s), 2220(s), 1670(s), 1200(s) (Found: C, 62.0; H, 8.1; N, 18.5. C₈H₁₂N₂O requires C, 63.2; H, 7.9; N, 18.4%).

1, 1-Diacetylcyclopropane III:

The reaction mixture on usual work-up gave III, yield 9g, (71%), b.p. 60-65° / 10 mm: showed single peak in GLC and gave yellow DNP derivative (m.p. 244-45°); PMR (CDCl₃): 1.38(*s*, 4H, -CH₂-CH₂-), 2.15(*s*, 6H, 2×CH₃); MS: (rel. int.): *m/z* 126(14), 111(28), 69(39), 43(100); IR (neat): 3600-3300(br, m), 1690(s), 1280(s), 1160(s), 1100(s), 1050-1030(w), 1000(m) (Found: C, 67.0; H, 7.5. C₇H₁₀O₂ requires C, 66.6; H, 7.9%).

The solid residue left in distilling flask on chromatography over silica gel and elution with benzene-pet. ether (20:80) afforded bis-(2'-pent-2'-en 4'-one)- 1, 2-ethylene diether, the dimer of the enol CH₃-COCH=C(CH₃)-OCH₂CH₂O-(CH₃)C=CHCO CH₃, yield 1.2g, (5%), m.p. 160-61°; gave a light yellow DNP derivative (m.p. 203-5°); PMR (CDCl₃): 2.1(*s*, 6H, 2×CH₃); 2.2(*s*, 6H, 2×CH₃); 4.0(*s*, 4H, -CH₂-CH₂-), 5.45(*s*, 2H, 2×-COCH=C-O-); MS: (rel. int.): *m/z* 226(2), 183(1), 127(29), 126(16), 111(5), 87(16), 85(21), 43(100); IR (nujol): 2960(m), 1660(s), 1600-1550(br,s), 1070(s), (Found: C, 63.5; H, 7.6. C₁₂H₁₈O₄ requires C, 63.7; H, 7.6%).

(a) *With hydrobromic acid*: Treatment of III (0.04 mol) with HBr (48%; 3 ml) in the cold overnight afforded 3-acetyl-5-bromopentan-2-one (6.8g, 82%), m.p. 73°; DNP derivative: m.p. 165°, PMR (CDCl₃): 0.70-1.20(*m*, *J*=6Hz, 2H, C₄-H), 1.65(*s*, 6H, 2×CH₃); 2.3-2.75(*m*, *J*=8Hz, 2H, C₅-H), 3.15-3.65(*t*, *J*=6Hz, 1H, C₃-H-); MS: (rel. int.): *m/z* 207(1), 181(2), 167(8), 138(16), 123(11), 85(63), 69(18), 43(100), 41(16); IR (nujol): 3400-3000(br, m), 1640-1590(br,s), 1580-1500(br, s), 1270(s) (Found: C, 40.3; H, 5.1. C₇H₁₁BrO₂ requires C, 40.5; H, 5.3%).

(b) *With isopropylamine*: Treatment of III (0.05 mol) with isopropylamine (0.1 mol) in ethanol (50 ml) under reflux for 5 hr afforded 1, 1-diacetyl-3-isopropylaminopropane (IIIa) (4.5g, 48.5%), b.p. 105-

10°C/5 mm, PMR (CDCl₃): 0.65-0.83(*t*, *J*=7Hz, 2H, C₄-H), 1.0-1.75(*t*, *J*=8Hz, 6H, isopropyl 2×CH₃), 1.3-1.7(*m*, *J*=7Hz, 2H, 5-CH₂), 2.10(*s*, 3H, CH₃), 2.25(*s*, 3H, CH₃), 2.6-2.8(*t*, *J*=10Hz, 1H, C₃-H), 3.0-3.55[*m*, *J*=7Hz, 1H, CH(CH₃)₂], 7.55(*s*, 1H, -NH); MS (rel. int.): *m/z* 184(1), 154(36), 153(52), 139(10), 138(100), 110(31), 82(13), 43(34); IR (neat): 3600-3100(b, m), 1650-1600(b, s), 1550-1500(br, m), 1260(m), 1030(w). (Found: C, 64.9; H, 10.0; N, 7.3. C₁₀H₁₉NO₂ requires C, 64.9; H, 10.4; N, 7.6%).

(c) *Reduction of monoketal*: To a warm solution of III (0.088 mol) in digol (25 ml) was added KOH (10g) in digol (100) followed by 10 ml hydrazine hydrate in 50 ml digol during 1 hr. The reaction mixture was heated on a water bath for 4 hr and worked up after acidification to give 1-acetyl-1-ethylcyclopropane¹⁷ (6.35 g, 64.2%), b.p. 50-55°/15 mm; gave yellow DNP derivative: m.p. 256-257°; PMR (CDCl₃): 0.5-0.9(*m*, *J*=7Hz, 4H, -CH₂-CH₂-), 0.95-1.10(*t*, *J*=6Hz, 3H, -CH₂-CH₃), 1.2-1.7(*q*, *J*=8Hz, 2H, -CH₂CH₃), 1.9(*s*, 3H, -COCH₃); MS (rel. int.): *m/z* 112(66), 97(23), 87(16), 69(22), 43(100), 41(43); IR (neat): 3060(w), 2960(b, s), 2880(sh, s), 1680(m), 1170(s), 1140(w), 1040(s), 1010(m) (Found: C, 75.5; H, 10.5. C₇H₁₄O requires C, 75.0; H, 10.7%).

(d) *Reduction with sodium borohydride*: To compound III (0.058 mol) in MeOH (150 ml) was added NaBH₄ (5g) during 1 hr, and the reaction mixture stirred for 6 hr, kept overnight at room temperature and worked up as usual to give 1-acetyl-1-(1-hydroxyethyl)cyclopropane (4g, 50%), b.p. 70-75°/10 mm; PMR (CDCl₃): 0.9(*t*, *J*=5Hz, 2H, -CH₂), 1.0-1.20(*d*, *J*=8Hz, 3H, CH₃), 1.35(*s*, *H*), 2.10(*s*, *H*), 1.80(*s*, 3H, -COCH₃), 3.10(*s*, 1H, -CHOH), 3.50-3.90[*q*, *J*=6Hz, 1H, -CH-OH]; IR (neat): 3550-3300(br, m), 2990(m), 2890(m), 1680(sh, s), 1190(sh, m), 1040(m) (Found: C, 60.4; H, 8.8. C₇H₁₂O₂ requires C, 60.8; H, 8.7%).

1-Acetyl-1-benzoylcyclopropane (IV)

Usual work-up of the reaction mixture gave IV (12g, 66%), b.p. 90-95°/10 mm; PMR (CDCl₃): 1.3-1.45(*m*, 7Hz, 4H, -CH₂-CH₂-), 1.90(*s*, 3H, -COCH₃), 7.2-7.6(*m*, *J*=7Hz, 3H *m/p*-Ar-H), 7.7-8.0(*m*, *J*=5Hz, 2H, *o*-Ar-H); MS (rel. int.): *m/z* 188(13), 187(16), 173(9), 105(100), 77(58), 69(4), 43(35); IR (neat): 3500-3340(br, m), 3020-2990(br, m), 1720(s), 1680(s), 1325-1300(m), 1020(m) (Found: C, 76.6; H, 5.9. C₁₂H₁₂O₂ requires C, 76.6; H, 6.4%).

The solid residue obtained from the above distillation was chromatographed over silica gel using benzene-pet. ether (20:80) as eluant affording bis(-1'-phenyl-buten-3'-one)-1, 2-ethylene diether, the dimer of the enol, CH₃-CO-CH=C(C₆H₅)-O-CH₂-CH₂-O-

C(C₆H₅)=CH-COCH₃, yield 1.2g(4%), m.p. 181-83°; gave red DNP derivative: m.p. 193-95°; PMR (CDCl₃): 2.5(*s*, 6H, 2×CH₃), 4.25(*s*, 4H, -CH₂-CH₂-), 6.25(*s*, 2H, 2×-CO-CH=C-O-), 7.40-7.65(*m*, *J*=5Hz, 6H, *m/p*-Ar-H), 7.8-8.1(*m*, *J*=5Hz, 4H, *o*-Ar-H); MS (rel. int.): *m/z* 350(2), 289(4), 288(12), 191(59), 105(10), 87(100), 77(100), 43(100); IR (nujol): 3020(w), 2980(w), 1685(s), 1600(s), 1200(s) (Found: C, 75.0; H, 6.7. C₂₂H₂₂O₄ requires C, 75.4; H, 6.3%).

(a) *With isopropylamine*: Compound IV (0.05 mol) was refluxed with isopropylamine (0.1 ml) in ethanol (50 ml) for 5 hr. Usual work-up afforded 1-acetyl-1-benzoyl-3-isopropylaminopropane (IVa), yield 4.8g (39%); b.p. 120-25°/5 mm; IR (neat): 3500-3200(br, m), 3040-3020(w), 1720(s), 1680-1650(br, s), 1600(s), 1220(w), 1100(w), 1000(w) (Found: C, 72.6; H, 8.3; N, 5.9. C₁₅H₂₁NO₂ requires C, 72.9; H, 8.5; N, 5.6%).

Ethyl 1-acetylcyclopropane-1-carboxylate¹⁸ (V):

Yield 9.75g (62%), b.p. 78-80°/10 mm; PMR (CDCl₃): 1.15-1.35(*t*, *J*=7Hz, 4H, -CH₂-CH₂-), 1.40(*s*, 3H, ester CH₃), 2.45(*s*, 3H, -COCH₃), 4.1-4.4(*q*, *J*=8Hz, 2H, -CH₂), MS (rel. int.): *m/z* 156(8.8), 141(24), 128(8), 113(23), 111(41), 110(25), 86(50), 69(72), 43(100); IR (neat): 3600(v, w), 3020(w), 2990(m), 1720-1690(b, s), 1450(m), 1320-1310(v, m), 1190(m), 1020(m) (Found: C, 61.3; H, 7.8. C₈H₁₂O₃ requires C, 61.5; H, 7.7%).

(a) *With ammonia*: Compound V (0.032 mol) on refluxing with ammonia (8 ml, 28%) for 2 hr was converted into the amide, 1-acetyl-1-amidocyclopropane (2.2g, 50%), m.p. 48°, IR (nujol) 3000(w), 1700(s), 1630(s), 1450(m), 1270(s), 1060(s), 1000(w). (Found: C, 55.5; H, 6.9. C₆H₉NO₃ requires C, 55.69; H, 7.1; N, 11.0%).

(b) *With alc. KOH*: Compound V on keeping with KOH (3.0g) in ethanol (30) overnight gave 1-acetylcyclopropane-1-carboxylic acid (3.5g, 54.7%), m.p. 78°; IR (nujol): 1700(s), 1680(s), 1250(s), 1020(m) cm⁻¹.

General Procedure for Cleavage with Grignard reagents

The cyclopropane compounds (VIa-f) obtained¹⁹ from various α-methyldiazoacetophenones and α-methyldiazo 1-naphthoyl ketone with cyclohexene, 1,2-dihydronaphthalene, and the ketal of cyclohexen-3-one, were cleaved with methyl-, phenyl-, vinyl-²⁰ and allylmagnesium halides and the Grignard products decomposed with acid (H₂SO₄/HBr) and worked up. The product in each case on GLC analysis usually showed two dissimilar peaks with slightly different retention times (the olefin and the tertiary hydroxy

compound). The analysis was usually made after treatment with strong acid or POCl_3 .

(a) *Cleavage with methyl magnesium iodide*

The adduct VIa was reacted with Grignard reagent prepared from MeI (4.5g) and Mg (0.75g) in ether. The reaction mixture was stirred in the cold, then refluxed 0.5 hr allowed to stand and worked up. Column chromatography over silica gel using petroleum ether (60-80) as eluant gave a viscous liquid (60%), b.p. $163^\circ/4$ mm; PMR (CDCl_3): 1.20 (s, 3H, *cis*- CH_3), 1.25-1.95 (m, $J=5\text{Hz}$, 10H, cyclohexyl H), 2.0 (s, 3H, *trans*- CH_3), 5.45-5.6 (d, $J=7.5\text{Hz}$, 1H, *cis/trans*-olefinic protons), 7.3 (m, $J=6\text{Hz}$, 5H, Ar-H), MS (rel. int.): m/z 326(43), 281(50), 269(64), 231(53), 168(72), 155(87), 141(82), 131(71), 104(86), 77(100); IR (neat): 3025(w), 1595(s), 1495(m), 1445(w), 1380(m), 1250(m), 1150(m), 1120(m), 1070(w) (Found C, 54.8; H, 5.7. $\text{C}_{15}\text{H}_{19}\text{I}$ requires C, 55.2; H, 5.8%). It was identified as 2-(2'-iodocyclohexyl)-1-methyl-1-phenylethylene (VII).

(b) *With phenylmagnesium bromide*

The adduct VIa was treated with Mg (0.75g) and bromobenzene (3g) in ether solvent. After usual work up the product was chromatographed over silica gel using pet. ether as eluant to give 2-(2'-bromocyclohexyl)-1,1-diphenylethylene (VIII), yield 65%, m.p. 87° ; PMR (CDCl_3): 1.20 (hump, 10H, cyclohexyl H), 4.60 (d, $J=6\text{Hz}$, 1H, olefinic H), 7.3 (m, 10H, Ar-H); MS (rel. int.): m/z 340(25), 262(54), 231(55), 203(89), 168(65), 139(66), 107(85), 77(96), 76(100); IR (nujol): 3040(w), 2940(w), 2840(m), 1600(s), 1455(m), 1360(m), 1250(m), 1170(m), 1020(w), 850(m) (Found: C, 64.6; H, 6.3. $\text{C}_{15}\text{H}_{19}\text{Br}$ requires C, 64.3; H, 6.8%).

(c) *With vinylmagnesium bromide*

Compound VIa on treatment with Mg (0.3) and vinyl bromide in THF followed by usual work up and column chromatography using petroleum ether (60-80) as eluant gave 4-(2'-bromocyclohexyl)-3 phenyl butadiene (IX) which crystallized from pet. ether, yield 40%, m.p. 112° ; PMR (CDCl_3): 1.40 (s, 10H, cyclohexyl H), 2.4-2.5 (d, $J=5\text{Hz}$, 2H, vinyl H), 2.9-3.1 (t, $J=6\text{Hz}$, 1H, olefinic H), 3.5 (d, $J=5\text{Hz}$, 1H, olefinic H), 7.5 and 8.0 (m, 5H, Ar-H), MS (rel. int.): m/z 201 (85), 157(64), 127(78), 120(98), 116(98), 105(91), 80(99), 77(100); IR (nujol): 3020(w), 2940(m), 1670(s), 1590(s), 1575(s), 1450(m), 1250(m), 1080(w), 770(m), 630(w).

(d) *With allylmagnesium bromide*

(i) 7-(4'-Chlorobenzoyl)norcarane (VIb) was treated with allylmagnesium bromide and the reaction worked up as described in the preceding case to give a binary liquid mixture (hydrated/dehydrated) (38%),

b.p. $155-160^\circ/5$ mm; PMR²¹ (CDCl_3): 0.7-1.0 (q, $J=6\text{Hz}$, 2H, $-\text{CH}_2-$, allylic), 1.05-2.7 (m, 9H, cyclohexyl H), 3.75 (s, 1H, C-2 cyclohexyl H), 4.85-5.2 (m, $J=7\text{Hz}$, 2H, allylic $=\text{CH}_2$), 5.35-5.9 (m, $J=4\text{Hz}$, 1H, allylic -CH), 7.20 (d, $J=4\text{Hz}$, 1H, olefinic H), 7.3-7.45 (m, 4H, Ar-H); MS (rel. int.): m/z 339(2), 237(32), 235(81), 169(12), 167(33), 152(22), 141(32), 139(100), 111(26), 81(47), 77(9), IR (neat): 3600-3200 (br, m), 1660-1640(m) 1590(sh, m), 1490(s), 1280(w), 1170(m), 780(w), 680(m) [Found: C, 59.4; H, 6.3. $\text{C}_{17}\text{H}_{20}\text{BrCl}$ (Xa) requires C, 60.0; H, 5.9%].

(ii) 7-(4'-Methoxybenzoyl)norcarane (VIb; 0.05 mol) on treatment with allylmagnesium bromide (0.076 mol) afforded a colourless liquid (36%), $150-53^\circ/5$ mm PMR (CDCl_3): 1.2-1.5 (t, $J=7\text{Hz}$, 2H, allylic $-\text{CH}_2$), 1.5-3.0 (m, 9H, cyclohexyl H), 3.75 (s, 3H, $-\text{OCH}_3$), 4.1-4.5 (m, 1H, cyclohexyl C_2 -H), 4.87-5.0 (m, $J=7\text{Hz}$, 2H, allylic $=\text{CH}_2$), 5.0-5.2 (d, $J=4\text{Hz}$, 1H, allylic -CH), 5.35-5.85 (m, 1H, olefinic H), 6.75-6.85 and 7.2-7.4 (m, 4H, Ar-H); MS (rel. int.): m/z 335(1), 178(13), 177(100), 136(39), 122(11), 121(14), 107(23), 91(23), 77(44); IR (neat): 3600-3150 (br, s), 3080-3000(br,s), 1635(s), 1600(s), 1450(b,s), 1250(s), 1170(m), 770(m), 690(m), 575(m). The product was identified as 5-(2'-bromocyclohexyl)-4 (4"-methoxyphenyl) -1,4-pentadiene (Xb) (Found: C, 65.0; H, 6.7. $\text{C}_{18}\text{H}_{23}\text{OBr}$ requires C, 64.5; H, 6.9%).

(iii) A similar treatment of 7-(α -naphthoyl)norcarane (VIe) in dry ether followed by decomposition with HBr and usual work up afforded 5-(2'-bromocyclohexyl)-4-(1"-naphthyl)-1,4-pentadiene (XI) as viscous yellow liquid (30%), b.p. $175-80^\circ/3$ mm; PMR (CDCl_3): 1.04 (t, $J=7\text{Hz}$, 2H, allylic $-\text{CH}_2$), 1.05-3.7 (m, 9H, cyclohexyl H), 3.7-4.1 (m, 1H, cyclohexyl C_2 -H), 4.8-5.2 (t, $J=6\text{Hz}$, 2H, allylic $=\text{CH}_2$), 5.25-5.45 (t, $J=5\text{Hz}$, 1H, allylic -CH), 5.48-6.05 (m, 1H, olefinic H), 7.28-8.0 (m, 7H, Ar-H); MS (rel. int.): m/z 355(24), 277(26), 275(29), 273(10), 234(100), 166(56), 154(4), 142(4), 80(4) (Found: C, 63.9; H, 7.2. $\text{C}_{18}\text{H}_{23}\text{OBr}$ requires C, 64.5; H, 6.9%).

(iv) The adduct VIId (0.05 mol) was reacted with allylmagnesium bromide (0.076 mol) at low temperature in ether. The reaction mixture on decomposition with HBr followed by usual work up afforded a thick liquid (31%), b.p. $160-165^\circ\text{C}/\text{mm}$; MS (rel. int.): m/z 164(1), 150(1), 136(7), 121(2), 105(28), 77(51), 51(22), 40(100); IR (neat): 3650-3100 (br, m), 3020(w), 1650(br, s), 1600(w), 1450(m), 1390(m), 1175 (w), 1100(m), 760(sh, m), 690(w), 650(w). The product was thus identified as 5-(2' bromocyclohexan 3'-one) 4-phenyl 1, 4 pentadiene (XII) (Found: C, 63.5; H, 6.2. $\text{C}_{17}\text{H}_{19}\text{OBr}$ requires C, 94.0; H, 6.0%).

(v) The cyclopropane derivative VIIf (0.005 mol) was treated with allylmagnesium bromide (0.02 mol) in

ether (200 ml) at 15-20°. The reaction mixture on decomposition with HBr followed by usual work up gave a thick liquid (34%), b.p. 175-89°/3 mm; MS (rel. int.): *m/z* 165(5), 149(12), 121(12), 105(22), 91(25), 77(20), 69(13), 51(12), 40(100), IR (neat): 3600-3120- (br, s), 3100(m), 300(s), 1600(m), 1490(s), 1360(m), 1250(m), 1170(s), 950(s), 760(s), 695(s), 570(m) (Found: C, 70.9; H, 6.1. C₂₁H₂₁Br requires C, 71.4; H, 6.0%). The product was identified as 5-[2'(1'-bromo 1', 2', 3', 4'-tetrahydro) naphthyl]-4-phenyl-1, 4-pentadiene (XIII).

Hydration

To the orange yellow suspension of VII (1g) in THF (5 ml) a solution of mercuric acetate (1g) in water (1 ml) and THF (1 ml) was added dropwise with stirring, till the colour was discharged. The mixture was stirred at room temperature for 1 hr and 3M NaOH (1ml) added under vigorous stirring followed by the addition of sodium borohydride (0.1g) in 1 ml 3M NaOH keeping the temperature below 25°. It was stirred further for 3 hr and allowed to stand overnight. The aq. alkaline layer (mercury layer) was separated from the organic layer and concentrated under reduced pressure. The organic layer was washed with water, dried over anhyd. CaSO₄ and solvent removed. The residue on distillation gave the hydrated olefin b.p. (0.3g), 140°/0.5 mm; PMR (CDCl₃): 0.82 (*hump*, 13H, CH₃ and cyclohexyl H), 1.22 (*m*, 2H, -CH₂), 7.35 (*m*, 5H, Ar-H); IR (neat): 3400(b,m), 3040(w), 2940 (m), 2890(m), 2840(m), 1450(m), 1350(m), 1280(m), 1150(m), 1080(w), 1000(w), 960(w), 880(w), 780(m), 730(m), 680(w) [Found: C, 52.8; H, 5.9. C₁₅H₂₁OI, 3-(2'-iodocyclohexyl)-2-hydroxy-2-phenylpropane (XIV) requires C, 52.3; H, 6.1%].

The olefins obtained above were generally mixtures of *trans/cis* as shown by PMR spectra. Also VIII and IX were found to be optically inactive.

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Regioselective Reactions of Tetra- & Penta-substituted Pyrroles†

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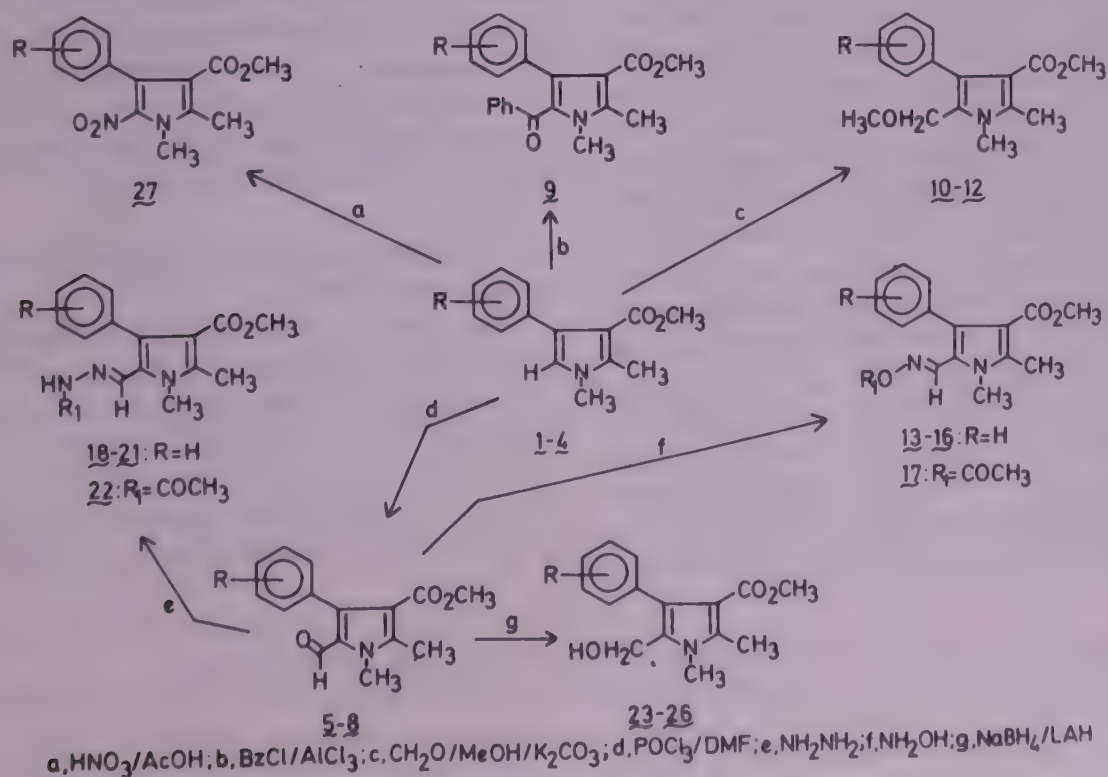
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Regioselective formylation, hydroxymethylation and benzylation in 1, 2-dimethyl-3-methoxycarbonyl-4-phenyl- or substituted phenyl-pyrroles (**1-4**) lead to the formation of the corresponding 5-substituted derivatives (**9-12**). Chemoselectivity in the reaction of 1, 2-dimethyl-5-formyl-3-methoxycarbonyl-4-phenyl or substituted phenyl-pyrroles (**5-8**) with hydroxylamine, hydrazine and lithium aluminium hydride has been observed. The reactions described here furnish a convenient method for the synthesis of pyrrole derivatives in which two electron withdrawing groups at positions 3 and 5 are present.

Studies on regioselective reaction of 1, 2-dimethyl-3-methoxycarbonyl-4-phenyl or substituted phenyl-pyrroles (**1-4**) are interesting because the substrates possess groups which can simultaneously take part in common organic reactions. For example, compounds **1-4** offer more than one site for formylation and Friedel-Craft reactions because aromatic substrates and pyrrole derivatives are attacked by electrophilic reagents^{1,2}. In compounds **5-8**, reactions with hydroxylamine, hydrazine and metal hydrides are of interest for ascertaining chemoselectivity in these reactions. The results obtained in these studies are record-

ed here.

The reaction of 2-nitro-1-substituted-phenylethylenes with methyl β -methylaminocrotonate at room temperature (25-30°) furnished compounds **1-4**. This reaction is slow and takes almost 72-96 hr for its completion. Attempts to accelerate it at elevated temperature invariably led to the formation of a number of products. Formylation of **1-4** with Vilsmeier reagent gave compounds **5-8** (Scheme 1). The absence of a PMR signal at δ 6.4 for the proton at C-5 in these pyrroles and the presence of a signal at δ 9.2 supported the assigned structures. This reaction is



Scheme 1

associated with polymerization and no compound with a formyl group on the phenyl ring could be isolated from the reaction mixture.

Reaction of **1** with benzoyl chloride in the presence of aluminium chloride gave **9** and the orientation of the benzoyl group was evident from the absence of the PMR signal at δ 6.4. However, this reaction with other substituents on the phenyl ring (**2-4**) led to extensive polymerization and the desired 5-aryoyl derivatives was not isolated. Under forcing conditions hydroxymethylation of compounds **1-3** in the presence of formaline and potassium carbonate in methanol yielded the compounds **10-12**. Structures of these compounds agreed well with their spectral data.

The formation of these compounds may be explained by two possible mechanisms. The first one relates to the formation of $\text{CH}_3\text{O}^+\text{CH}_2$ under the reaction conditions used and the second one is based on the formation of 5-hydroxymethyl derivative followed by elimination of water and addition of methanol. In order to ascertain this, **23** was refluxed with potassium carbonate in methanol for several hours but the formation of **10** was not observed. However, the reaction of **2** with formalin and potassium carbonate in methanol furnished **10**. It, therefore, appears that $\text{CH}_3\text{OCH}_2^+$ is generated under the reaction conditions for the formation of compounds **10-12**.

Reactions of **5-8** with hydroxylamine hydrochloride and hydrazine hydrate yielded the oximes (**13-16**) and hydrazones (**18-21**) respectively. In none of the cases the methoxycarbonyl group was affected. The stereochemistry of the oximes across the C—C bond at position-5 of pyrrole ring was worked out by studying Nuclear Overhauser effect on the aldoxime proton ($\text{CH}=\text{N}$) in one of the representative compound (**13**). The N-methyl protons experienced 15% NOE when the aldoxime proton at δ 7.6 was irradiated. This suggested a close proximity between the $\text{CH}=\text{N}$ and N-methyl protons in space. The stereochemistry across the C=N bond in the oxime **13** was evident from a comparative study of the PMR spectra of **13** and its acetate (**17**). The downfield shift of methine proton by 20 Hz indicated the *E*-stereochemistry of the oxime. It was, therefore, evident that the formation of oximes (**13-16**) was stereoselective. Unlike the acetate (**17**), the acetate of hydrazone (**22**) was found to be a mixture of two stereoisomers.

Lithium aluminium hydride reduction of **5** gave **23** in 40% yields along with polymeric materials, and was purified by fractional crystallization from methanol. However, LAH reduction of **6-8** gave the desired alcohols (**24-26**) in extremely small amounts and the starting aldehyde could be obtained after column chromatography of the crude reduction products. In

order to explain the poor yields of **24-26**, the pure alcohols **24-26**, obtained by borohydride reduction of **6-8**, were chromatographed over silica gel. It was observed that the alcohols **24-26** were partly oxidised on the column to yield **6-8** along with several other products. The shelf life of the alcohols was found to be poor and these did undergo aerial oxidation to the corresponding aldehydes. Therefore, the low yields of **24-26** from the LAH reduction of **6-8** could be attributed to the instability of the alcohols on silica gel column.

Nitration of **1** and **4** were studied in greater details. Despite the fact that 1,2-dimethoxy-4-nitrobenzene is capable of yielding 4,5-dinitro derivatives, the nitration of **4** yielded only the 5-nitropyrrole derivative (**27**). Nitration of compound **1** gave a number of products and purification of these products was difficult. However, the mass spectrum of the crude reaction mixture did not indicate the formation of a dinitro derivative.

Conventional syntheses of pyrroles do not provide an opportunity to obtain compounds in which two electron withdrawing groups are present at positions 3 and 5. The reactions described herein have furnished an easy access to this class of compounds.

Experimental Procedure

Melting points were determined on an electrically heated block and are uncorrected. All the compounds were routinely checked for their structures by elemental analyses and spectral (PMR and IR) data (Table I). IR spectra were recorded on a Perkin-Elmer 157 infracord (ν_{max} in cm^{-1}), PMR spectra on an R-32 or EM-360L spectrometer using TMS as internal standard (chemical shift in δ , ppm) and mass spectra on a Jeol-JMS-D-300 instrument.

1, 2-Dimethyl-3-methoxycarbonyl-4-(substituted phenyl)pyrroles (1-4)

To a solution of methyl β -methylaminocrotonate (0.033 mol) in methanol (25 ml) was added 2-nitro-1-(substituted phenyl)ethylene (0.03 mol) with stirring at room temperature (25–30°). The reaction mixture was further stirred for 72–96 hr, poured on to crushed ice and left overnight. The separated solid was filtered, dried and recrystallized from aq. methanol.

1, 2-Dimethyl-5-formyl-3-methoxycarbonyl-4-(substituted phenyl)pyrroles (5-8)

To a mixture of DMF (7.0 ml) and POCl_3 (3.0 ml) at 0° under stirring was added the appropriately substituted pyrrole (**1-4**, 0.01 mol) and the reaction mixture left at 0° for 17–20 hr. In case of compound **4** the reaction mixture was left at room temperature (30°) for 24 hr. It was then poured on to crushed ice and the

Table I—Physical and Spectral Data of the Compounds 1-27

Compd	R	m.p. °C	Yield (%)	Mol. formula*	MS <i>m/z</i> (M ⁺)	IR(KBr) cm ⁻¹	PMR(δ , ppm)
1	H	77-78	70	C ₁₄ H ₁₅ NO ₂	229	1685 (CO ₂ CH ₃)	CDCl ₃ : 2.43 (s, 3H, 2-CH ₃), 3.42 (s, 3H, N-CH ₃), 3.55 (s, 3H, -CO ₂ -CH ₃), 6.39 (s, 1H, H-5), 7.00-7.32 (<i>m</i> , 5H, Ar- <i>H</i>).
2	3, 4-(OCH ₃) ₂ O	95-96	65	C ₁₆ H ₁₉ NO ₄	289	1685 (CO ₂ CH ₃)	CDCl ₃ : 2.44 (s, 3H, 2-CH ₃), 3.45 (s, 3H, N-CH ₃), 3.59 (s, 3H, -CO ₂ -CH ₃), 3.75 (<i>bs</i> , 6H, 2×OCH ₃), 6.40 (s, 1H, H-5), 6.70-6.90 (<i>m</i> , 3H, Ar- <i>H</i>).
3	3, 4-OCH ₂ O-	77-78	60	C ₁₅ H ₁₅ NO ₄	273	1685 (CO ₂ CH ₃)	CDCl ₃ : 2.40 (s, 3H, 2-CH ₃), 3.40 (s, 3H, N-CH ₃), 3.57 (s, 3H, -CO ₂ -CH ₃), 5.81 (s, 2H, O-CH ₂ -O), 6.42 (s, 1H, H-5), 6.65-6.80 (<i>m</i> , 3H, Ar- <i>H</i>).
4	2-NO ₂ -4, 5-(OCH ₃) ₂	177-78	50	C ₁₆ H ₁₈ N ₂ O ₆	334	1695 (CO ₂ CH ₃)	CDCl ₃ : 2.40 (s, 3H, 2-CH ₃), 3.50 (<i>bs</i> , 6H, N-CH ₃ and -CO ₂ -CH ₃), 3.85 and 3.90 (2s, 6H, 2×OCH ₃), 6.46 (s, 1H, H-5), 6.70 (s, 1H, 6'-Ar <i>H</i>) 7.58 (s, 1H, 3'-Ar <i>H</i>).
5	H	71-72	64	C ₁₅ H ₁₅ NO ₃	257	1685 (CHO), 1650 (CO ₂ CH ₃)	CDCl ₃ : 2.53 (s, 3H, 2-CH ₃), 3.50 (s, 3H, N-CH ₃), 3.90 (s, 3H, -CO ₂ -CH ₃), 7.20-7.42 (<i>m</i> , 5H, Ar- <i>H</i>), 9.16 (s, 1H, 5-CHO).
6	3, 4-(OCH ₃) ₂	117-18	50	C ₁₇ H ₁₉ NO ₅	317	1720 (CHO), 1655 (CO ₂ CH ₃)	CDCl ₃ : 2.52 (s, 3H, 2-CH ₃), 3.55 (s, 3H, N-CH ₃), 3.80, 3.84 and 3.90 (3s, 9H, 2×OCH ₃ and CO ₂ CH ₃), 6.80 (<i>bs</i> , 3H, Ar- <i>H</i>), 9.25 (s, 1H, 5-CHO).
7	3, 4-OCH ₂ O-	166-67	50	C ₁₆ H ₁₅ NO ₅	301	1680 (CHO), 1635 (CO ₂ CH ₃)	CDCl ₃ : 2.52 (s, 3H, 2-CH ₃), 3.58 (s, 3H, N-CH ₃), 3.90 (s, 3H, CO ₂ CH ₃), 5.93 (s, 2H, OCH ₂ O), 6.56-6.72 (<i>bs</i> (s), 3H, Ar- <i>H</i>), 9.22 (s, 1H, 5-CHO).
8	2-NO ₂ -4, 5-(OCH ₃) ₂	164-65	50	C ₁₇ H ₁₈ N ₂ O ₇	362	1715 (CHO), 1665 (CO ₂ CH ₃)	CDCl ₃ : 2.53 (s, 3H, 2-CH ₃), 3.48 (s, 3H, N-CH ₃), 3.80-3.96 (<i>m</i> , 9H, 2×OCH ₃ and CO ₂ CH ₃), 6.62 (s, 1H, 6'-Ar- <i>H</i>), 7.66 (s, 1H, 3'-Ar- <i>H</i>), 9.14 (s, 1H, 5-CHO).
9	H	77-78	30	C ₂₁ H ₁₉ N ₂ O ₃	333	1685 (CH ₂ CH ₃), 1630 (CO)	CCl ₄ : 2.54 (s, 3H, 2-CH ₃), 3.37 (s, 3H, N-CH ₃), 3.66 (s, 3H, CO ₂ CH ₃), 6.75-7.35 (<i>m</i> , 10H, Ar- <i>H</i>).
10	H	82-83	70	C ₁₆ H ₁₉ NO ₃	273	1690 (CO ₂ CH ₃)	CDCl ₃ : 2.45 (s, 3H, 2-CH ₃), 3.10 (s, 3H, N-CH ₃), 3.44 (<i>bs</i> , 6H, CO ₂ CH ₃ and OCH ₃), 4.1 (s, 2H, 5-CH ₂), 7.18 (<i>bs</i> , 5H, Ar- <i>H</i>).
11	3,4(OCH ₃) ₂	Oil	52	C ₁₈ H ₂₃ NO ₅	333	1680* (CO ₂ CH ₃)	CDCl ₃ : 2.50 (s, 3H, 2-CH ₃), 3.16 (s, 3H, N-CH ₃), 3.48 and 3.52 (2s, CO ₂ CH ₃ and OCH ₃), 3.78 and 3.82 (2s, 6H, 2×OCH ₃ Arom), 4.15 (s, 2H, 5-CH ₂), 6.78 (<i>bs</i> , 3H, Ar- <i>H</i>).
12	3,4-OCH ₂ O-	Oil	50	C ₁₇ H ₁₉ NO ₅	317	1690† (CO ₂ CH ₃)	CDCl ₃ : 2.41 (s, 3H, 2-CH ₃), 3.15 (s, 3H, N-CH ₃), 3.46 and 3.49 (2s, 6H, CO ₂ CH ₃ OCH ₃), 4.17 (s, 2H, 5-CH ₂), 5.87 (s, 2H, OCH ₂ O), 6.54-6.70 (<i>m</i> , 3H, Ar- <i>H</i>).
13	H	198-99	90	C ₁₅ H ₁₆ N ₂ O ₃	272	1680 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 2.48 (s, 3H, 2-CH ₃), 3.44 (s, 3H, N-CH ₃), 3.77 (s, 3H, CO ₂ CH ₃), 7.00-7.30 (<i>m</i> , 5H, Ar- <i>H</i>), 7.60 (s, 1H, 5-CH).
14	3,4(OCH ₃) ₂	176-77	90	C ₁₇ H ₂₀ N ₂ O ₅	332	1680 (CO ₂ CH ₃)	CDCl ₃ : 2.47 (s, 3H, 2-CH ₃), 3.48 (s, 3H, N-CH ₃), 3.70, 3.73 and 3.80 (3s, 9H, CO ₂ CH ₃ and 2×OCH ₃), 6.52-6.80 (<i>m</i> , 3H, Ar- <i>H</i>), 7.70 (<i>m</i> , 3H, 5-CH).
15	3,4-OCH ₂ O-	189-90	75	C ₁₆ H ₁₆ N ₂ O ₅	316	1685 (CO ₂ CH ₃)	CCl ₄ + CDCl ₃ : 2.48 (s, 3H, 2-CH ₃), 3.49 (s, 3H, N-CH ₃), 3.72 (s, 3H, CO ₂ CH ₃), 5.86 (s, 2H, OCH ₂ O), 6.50-6.70 (<i>m</i> , 3H, Ar- <i>H</i>), 7.64 (s, 1H, 5-CH).
16	2, NO ₂ -4,5-(OCH ₃) ₂	177-78	70	C ₁₇ H ₁₉ N ₃ O ₇	377	1670 (CO ₂ CH ₃)	CDCl ₃ : 2.48 (s, 3H, 2-CH ₃), 3.42 (s, 3H, N-CH ₃), 3.70, 3.79 and 3.88 (3s, 9H, CO ₂ CH ₃ and 2×OCH ₃), 6.52-6.80 (<i>m</i> , 3H, Ar- <i>H</i>), 7.70 (<i>m</i> , 3H, 5-CH).

(Contd.)

Table 1—Physical and Spectral Data of the Compounds 1-27—Contd

Compd	R	m.p. °C	Yield (%)	Mol. formula*	MS $m/z(M^+)$	IR(KBr) cm^{-1}	PMR (δ , ppm)
17	H	127-28	75	C ₁₇ H ₁₈ N ₂ O ₄	314	1690 (CO ₂ CH ₃)	and 2×OCH ₃), 6.51 (<i>s</i> , 1H, 6'-Ar- <i>H</i>), 7.58 (<i>bs</i> , 2H, 3'-Ar- <i>H</i> and 5-CH). CDCl ₃ : 2.00 (<i>s</i> , 3H, COCH ₃), 2.50 (<i>s</i> , 3H, 2-CH ₃), 3.46 (<i>s</i> , 3H, N-CH ₃), 3.86 (<i>s</i> , 3H, CO ₂ CH ₃), 7.00-7.35 (<i>m</i> , 5H, Ar- <i>H</i>), 7.81 (<i>s</i> , 1H, 5-CH).
18	H	190-91	80	C ₁₅ H ₁₇ N ₃ O ₂	271	1655 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 2.47 (<i>s</i> , 3H, 2-CH ₃), 3.43 (<i>s</i> , 3H, N-CH ₃), 3.77 (<i>s</i> , 3H, CO ₂ CH ₃), 5.70 (<i>bs</i> , 2H, NH ₂), 7.02-7.25 (<i>m</i> , 5H, Ar- <i>H</i>), 7.32 (<i>s</i> , 1H, 5-CH).
19	3, 4-(OCH ₃) ₂	169-70	75	C ₁₇ H ₂₁ N ₃ O ₄	331	1695 (CO ₂ CH ₃)	CDCl ₃ : 2.46 (<i>s</i> , 3H, 2-CH ₃), 3.46 (<i>s</i> , 3H, N-CH ₃), 3.70, 3.74 and 3.80 (3 <i>s</i> , 9H, CO ₂ CH ₃ and 2×OCH ₃), 5.08 (<i>bs</i> , 2H, NH ₂), 6.60-6.75 (<i>m</i> , 3H, Ar- <i>H</i>), 7.32 (<i>s</i> , 1H, 5-CH).
20	3, 4-OCH ₂ O-	200-01	75	C ₁₆ H ₁₇ N ₃ O ₄	315	1675 (CO ₂ CH ₃)	CDCl ₃ : 2.46 (<i>s</i> , 3H, 2-CH ₃), 3.50 (<i>s</i> , 3H, N-CH ₃), 3.76 (<i>s</i> , 3H, CO ₂ CH ₃), 5.88 (<i>s</i> , 2H, OCH ₂ O), 6.52-6.75 (<i>m</i> , 3H, Ar- <i>H</i>), 7.34 (<i>s</i> , 1H, 5-CH).
21	4-NO ₂ -4, 5-(OCH ₃) ₂	176-77	88	C ₁₇ H ₂₀ N ₄ O ₆	376	1685 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 2.51 (<i>s</i> , 3H, 2-CH ₃), 3.43 (<i>s</i> , 3H, N-CH ₃), 3.79, 3.82 and 3.90 (3 <i>s</i> , 9H, CO ₂ CH ₃ and 2×OCH ₃), 5.58 (<i>bs</i> , 2H, NH ₂), 6.60 (<i>s</i> , 1H, 6'-Ar- <i>H</i>), 7.28 (<i>s</i> , 1H, 3'-Ar- <i>H</i>), 7.56 (<i>s</i> , 1H, 5-CH).
22	H	160-61	80	C ₁₇ H ₁₉ N ₃ O ₃	313	1680 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 1.86 and 2.10 (2 <i>s</i> , 3H, COCH ₃), 2.50 (<i>s</i> , 3H, 2-CH ₃), 3.45 (<i>s</i> , 3H, N-CH ₃), 3.83 and 3.90 (2 <i>s</i> , 3H, CO ₂ CH ₃), 7.02-7.40 (<i>m</i> , 5H, Ar- <i>H</i>), 7.55 and 7.65 (2 <i>s</i> , 1H, 5-CH).
23	H	174-75	85	C ₁₅ H ₁₇ NO ₃	259	1665 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 2.47 (<i>s</i> , 3H, 2-CH ₃), 3.46 (<i>s</i> , 3H, N-CH ₃), 3.56 (<i>s</i> , 3H, CO ₂ CH ₃), 4.23-4.33 (<i>d</i> , 2H, 5-CH ₂), 4.46-4.62 (<i>t</i> , 1H, OH), 7.18 (<i>bs</i> , 5H, Ar- <i>H</i>).
24	3, 4-(OCH ₃) ₂	164-65	70	C ₁₇ H ₂₁ NO ₅	319	1690 (CO ₂ CH ₃)	CDCl ₃ +DMSO- <i>d</i> ₆ : 2.43 (<i>s</i> , 3H, 2-CH ₃), 3.48 and 3.52 (2 <i>s</i> , 6H, CO ₂ CH ₃ and N-CH ₃), 3.72 and 3.78 (2 <i>s</i> , 6H, 2×OCH ₃), 4.24-4.33 (<i>m</i> , 2H, 5-CH ₂), 4.39-4.50 (<i>t</i> , 1H, OH), 6.70-6.83 (<i>m</i> , 3H, Ar- <i>H</i>).
25	3, 4-OCH ₂ O-	154-55	50	C ₁₆ H ₁₇ NO ₅	303	1660 (CO ₂ CH ₃)	CDCl ₃ : 2.44 (<i>s</i> , 3H, 2-CH ₃), 3.48 (<i>bs</i> , 6H, N-CH ₃ and CO ₂ CH ₃), 4.32 (<i>bs</i> , 2H, 5-CH ₂), 5.85 (<i>s</i> , 2H, 5-CH ₂), 5.85 (<i>s</i> , 2H, OCH ₂ O), 6.55-6.75 (<i>m</i> , 3H, Ar- <i>H</i>).
26	2-NO ₂ -4, 5-(OCH ₃) ₂	94-95	50	C ₁₇ H ₂₀ N ₂ O ₇	364	1680 (CO ₂ CH ₃)	CDCl ₃ : 2.44 (<i>s</i> , 3H, 2-CH ₃), 3.40 (<i>s</i> , 3H, N-CH ₃), 3.51 (<i>s</i> , 3H, CO ₂ CH ₃), 3.76 and 3.84 (2 <i>s</i> , 6H, 2×OCH ₃), 4.24 (<i>bs</i> , 2H, 5-CH ₂), 6.57 (<i>s</i> , 1H, 6'-Ar- <i>H</i>), 7.46 (<i>s</i> , 1H, 3'-Ar- <i>H</i>).
27	2-NO ₂ -4, 5-(OCH ₃) ₂	112-13	53	C ₁₆ H ₁₇ N ₃ O ₈	379	1690 (CO ₂ CH ₃)	CDCl ₃ : 3.03 (<i>s</i> , 3H, 2-CH ₃), 3.72 (<i>s</i> , 3H, N-CH ₃), 3.84, 3.88 and 3.92 (3 <i>s</i> , 9H, CO ₂ CH ₃ and 2×OCH ₃), 6.84 (<i>s</i> , 1H, 6'-Ar- <i>H</i>), 7.70 (<i>s</i> , 1H, 3'-Ar- <i>H</i>).

*All the compounds gave satisfactory, C, H and N analyses.
†IR (neat)

solid filtered. The filtrate was left in a refrigerator for 48-72 hr to obtain the additional amounts of appropriate formyl derivatives. These compounds were recrystallized from methanol.

5-Benzoyl-1, 2-Dimethyl-3-methoxycarbonyl-4-phenylpyrroles (9)

To a mixture of 1 (0.002 ml) and benzoyl chloride (0.010 mol) was added anhyd. AlCl₃ (0.005 mol) at

room temperature (32°) with stirring. After 24 hr, the reaction mixture was poured on to crushed ice and extracted with ethyl acetate. Usual work-up of the organic layer furnished a residue which was purified by chromatography over a silica gel column using hexane-chloroform as eluant.

1, 2-Dimethyl-3-methoxycarbonyl-5-methoxymethyl-4-(substituted phenyl)pyrroles (10-12)

A mixture of **1-3** (0.002 mol), formalin (aq. 40%, 4.0 ml) and potassium carbonate (0.004 mol) in methanol (10 ml) was heated in a steel-bomb at 120-30° for 24 hr. Reaction mixture was diluted with water, and the separated solid filtered and recrystallized from aq. methanol. In cases where no solid precipitated out, the reaction mixture was extracted with ethyl acetate and the usual work-up of the organic layer furnished a residue which was purified by preparative TLC.

1, 2-Dimethyl-3-methoxycarbonyl-4-(substituted phenyl)pyrroles 5-aldoximes (13-16)

To a solution of **5-8** (0.005 mol) in methanol (15 ml) under stirring were added hydroxylamine hydrochloride (0.0075 mol) and anhyd. sodium acetate (0.0075 mol). The reaction mixture was further stirred at room temperature (29-32°) for 14-17 hr and poured on to crushed ice. The separated solid was filtered, washed with water, dried and recrystallized from methanol.

1, 2-Dimethyl-3-methoxycarbonyl-4-phenylpyrrole-5-aldoxime acetate (17)

To a cold mixture of **13** (0.001 mol) and acetic anhydride (0.01 mol) under stirring was added pyridine (1 drop). The reaction mixture was further stirred at 5-10° for 4 hr and poured on to crushed ice. The precipitated solid was filtered, dried and recrystallized from aq. methanol.

1, 2-Dimethyl-3-methoxycarbonyl-4-(substituted phenyl)pyrrole-5-formyl hydrazones (18-21)

To a solution of **5-8** (0.005 mol) in methanol (15 ml) was added hydrazine hydrate (0.015 mol) and the reaction mixture stirred at room temperature (30-32°) for 15-22 hr, diluted with water and the separated solid filtered, dried and recrystallized from chloroform-hexane.

1, 2-Dimethyl-3-methoxycarbonyl-4-phenylpyrrole-5-formyl acetylhydrazone (22)

The experimental procedure was essentially the same as described for **17**. The starting material was **18**.

1, 2-Dimethyl-5-hydroxymethyl-3-methoxycarbonyl-4-(substituted phenyl)pyrroles (23-26)

Method-A

To a solution of **5-8** (0.006 mol) in methanol (15 ml) under stirring was added sodium borohydride (0.024 mol) in small fractions at 0.3°. The reaction mixture was then stirred at room temperature (30-32°) for 20-40 hr and poured on to crushed ice. The separated solid was filtered, dried and recrystallized from methanol.

Method-B

To a suspension of lithium aluminium hydride (0.002 mol) in dry ether (5 ml) or dry tetrahydrofuran (5 ml) under stirring was added the appropriate aldehyde (**5-8**; 0.001 mol). The reaction mixture was then refluxed for 8-20 hr, cooled to room temperature (31-32°) and extracted with ethylacetate. Usual work-up of organic layer furnished a residue which was purified either by recrystallization from methanol (compound **23**; yield 40-45%) or by chromatography over a silica gel column (compounds **24-26**; yield 2-5%).

1, 2-Dimethyl-3-methoxycarbonyl-5-nitro-4-(4, 5-dimethoxy-2-nitrophenyl)pyrrole (27)

To a cold mixture of **4** (0.001 mol), gl. acetic acid (2.0 ml) and potassium nitrate (0.004 mol) under stirring was added conc. H₂SO₄ (0.2 ml). The reaction mixture was then heated under stirring at 50-60° for 6 hr, cooled and poured on to crushed ice. The separated solid was filtered dried and recrystallized from methanol.

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Synthesis & Biological Activities of Isoxazolo [5,4-*d*] pyrimidinyl-oxymethyl-thiadiazoles, -oxadiazoles & -triazoles

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A series of new 5-[(3'-substituted isoxazolo [5,4-*d*]pyrimidin-4'-yl) oxymethyl]-1,3,4-thiadiazoles (Va-f), -1,3,4-oxadiazoles (VIa-f, VIIa-c) and -1,2,4-triazoles (VIIa-f) have been synthesised from 4-hydroxy-3-substituted-isoxazolo [5,4-*d*]pyrimidines (Ia-c) through N¹-(3'-substituted-isoxazolo [5,4-*d*]pyrimidin-4-yloxyacetyl)-N⁴-(substituted phenyl)-3-thiosemicarbazides (IVa-f). These thiosemicarbazides (IVa-f) have been readily obtained from (3-substituted isoxazolo [5,4-*d*]pyrimidin-4-yl)oxyacetic acid hydrazides (IIIa-c) in good yields. Structures of the new compounds have been established by their elemental analyses and spectral data. Some of the compounds show marked antibacterial and antifungal activities. Structure activity relationship has also been studied.

Recently isoxazolo [5,4-*d*]pyrimidines have been shown to possess significant antibacterial^{1,2} and analgesic³ activities. It is well established that various derivatives of 1,3,4-thiadiazole, 1,3,4-oxadiazole and 1,2,4-triazole exhibit interesting pharmacological properties like antitubercular^{4,5}, bacteriostatic^{6,7}, hypoglycemic⁸, diuretic⁹, antiinflammatory¹⁰, antiviral¹¹ and antifungal^{12,13} activities. Also, 1-aceyl-4-substituted-thiosemicarbazides and acid hydrazides have been found to possess a side spectrum of medicinal activities which include antitubercular⁵, antibacterial and antifungal activities¹⁴. These observations prompted us to synthesise the title compounds wherein biologically active moieties are present and evaluate them and their intermediates for antibacterial, antifungal and antitubercular activities.

The reaction sequence leading to the formation of different title compounds are outlined in Scheme 1. The reaction of 4-hydroxy-3-substituted-isoxazolo [5,4-*d*]pyrimidines (Ia-c) with ethyl chloroacetate in the presence of dry acetone and anhyd. K₂CO₃ yielded the desired ethyl (3-substituted isoxazolo [5,4-*d*]pyrimidines-4-yloxy)acetates (IIa-c) in good yields. These esters (IIa-c) were converted into (3-substituted isoxazolo [5,4-*d*]pyrimidines-4-yl)oxyacetic acid hydrazides (IIa-c) by treatment with a slight excess of 99% hydrazine hydrate in abs. ethanol under reflux. The precursors (IVa-f) were conveniently synthesised by refluxing acid hydrazides (IIIa-c) with *p*-substituted-phenyl isothiocyanates in ethanol for 2 hr.

The thiosemicarbazides (IVa-f) were readily cyclised to 5-[(3'-substituted isoxazolo [5,4-*d*]pyrimidine-4'-yl)oxymethyl]-2-(substituted phenylamino)-1,3,4-thiadiazoles (Va-f) by heating with anhyd. orthophos-

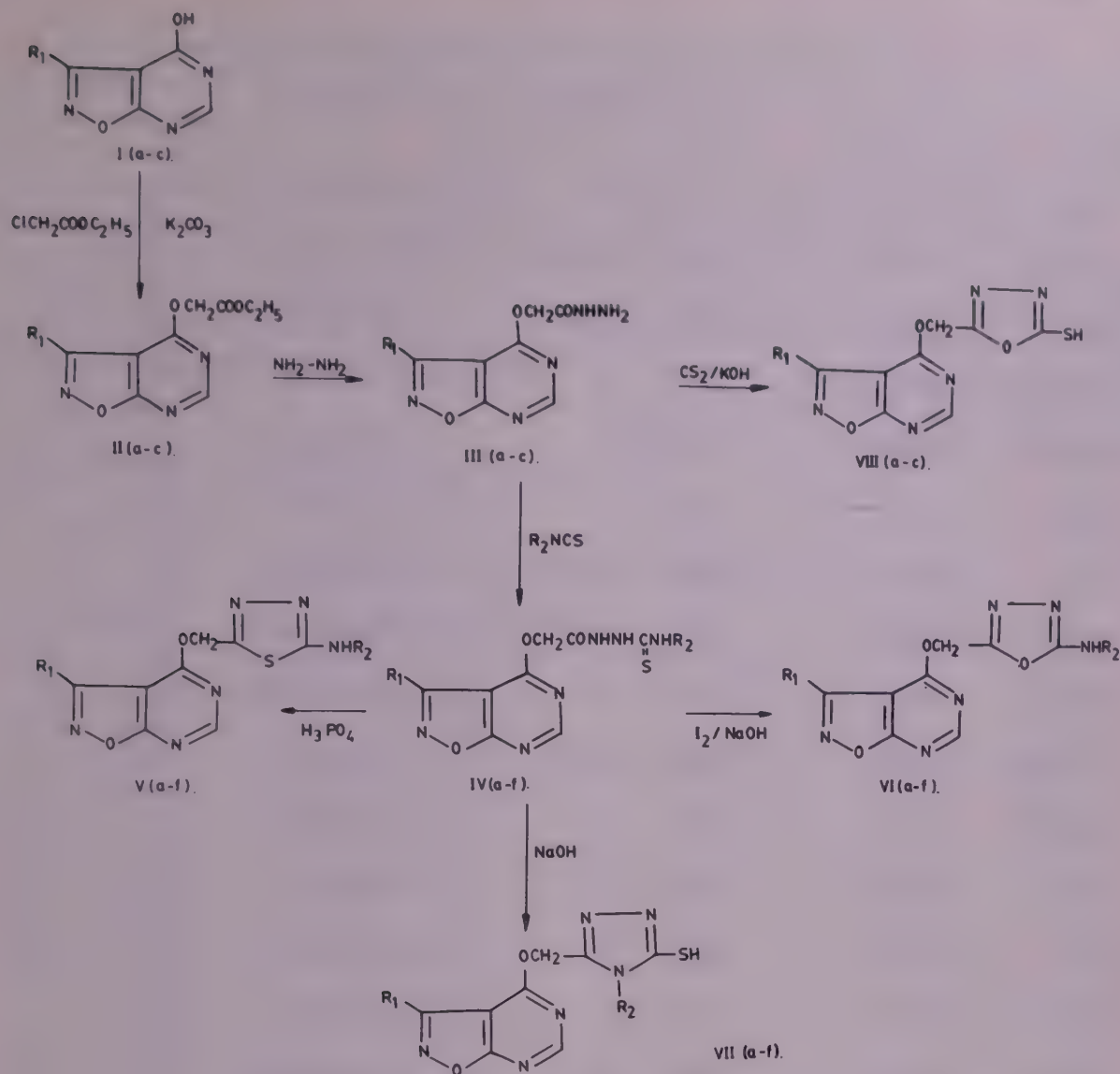
phoric acid at 120° for 30 min. 5-[(3'-Substituted isoxazolo[5, 4-*d*]pyrimidin-4'-yl)oxymethyl]-2-(substituted phenylamino)-1, 3, 4-oxadiazoles (VIa-f) were obtained by oxidative cyclisation of IVa-f using iodine and potassium iodide in ethanolic NaOH¹⁵. The thiosemicarbazides (IVa-f) on heating with 4% NaOH solution of 1 hr, underwent smooth cyclisation to afford 5-[(3'-substituted isoxazolo [5,4-*d*]pyrimidin-4'-yl)oxymethyl]-4-(substituted phenyl)-4*H*-1, 2, 4-triazole-2-thiols (VIIa-f). Further, 5-[(3'-substituted isoxazolo [5,4-*d*]pyrimidin-4'-yl)oxymethyl]-2-mercapto-1, 3, 4-oxadiazoles (VIIIa-c) were synthesised from (3-substituted isoxazolo [5, 4-*d*]pyrimidine-4-yloxy)-acetic acid hydrazides (IIIa-c) by heating with CS₂ and ethanolic KOH for 6 hr.

Structures of all the new compounds synthesised (Table I) were established by their elemental analyses and spectral data. The IR, PMR and mass spectral data of some representative compounds are given in experimental part.

Biological evaluation

All the compounds synthesised were evaluated for their *in vitro* antibacterial activity against the pathogenic microorganisms *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae* (all gram-negative) and *Staphylococcus aureus* (gram-positive) using paper disc diffusion method¹⁶. Sterilized 10 mm paper disc impregnated with 0.1 ml of the drug solution (200 µg in DMF) was placed in the petridish containing 25-30 ml of nutrient agar inoculated with 18-24 hr test culture. Incubation was carried out at 37° for 24 hr and zone of inhibition was measured in mm. Antifungal activity of the compounds was determined *in vitro* against *Aspergillus niger*, *Candida albicans* and *Aspergillus flavus*, adopting the turbidity method¹⁷. In the

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Scheme 1

Table 1—Characterization Data of the Compounds II-VIII

Compd	R_1	R_2	m.p. °C	Crystallised from*	Yield (%)	Mol. formula	Found (%) (Calc)		
							C	H	N
IIa	C_6H_5		165-66	E	82	$\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$	60.5 (60.2)	4.2 (4.3)	14.4 (14.0)
IIb	4- ClC_6H_4		204-5	M	85	$\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}_4$	53.7 (53.9)	3.9 (3.6)	12.4 (12.5)
IIc	4- $\text{CH}_3\text{C}_6\text{H}_4$		186-87	E	79	$\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4$	61.2 (61.4)	4.8 (4.8)	13.5 (13.4)
IIIa	C_6H_5		122-23	B	61	$\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_3$	52.0 (51.8)	4.1 (3.9)	24.3 (24.6)
IIIb	4- ClC_6H_4		201-2	B	67	$\text{C}_{13}\text{H}_{10}\text{ClN}_5\text{O}_3$	48.7 (48.9)	3.0 (3.1)	22.1 (21.9)
IIIc	4- $\text{CH}_3\text{C}_6\text{H}_4$		259(d)	B	63	$\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_3$	56.0 (56.2)	4.5 (4.3)	23.3 (23.4)
IVa	C_6H_5	4- $\text{CH}_3\text{C}_6\text{H}_4$	128-29 (d)	M	74	$\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_3\text{S}$	57.9 (58.1)	4.3 (4.1)	19.2 (19.3)

(Contd.)

Table 1—Characterization Data of the Compounds II-VIII —Contd

Compd	R ₁	R ₂	m.p. °C	Crystallised from*	Yield (%)	Mol. formula	Found (%) (Calc)		
							C	H	N
IVb	C ₆ H ₅	4-BrC ₆ H ₄	195-96	E	72	C ₂₀ H ₁₅ BrN ₆ O ₃ S	48.4 (48.1)	2.8 (3.0)	16.6 (16.8)
IVc	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	196-97	D(aq)	75	C ₂₁ H ₁₇ ClN ₆ O ₃ S	54.0 (53.8)	3.8 (3.6)	17.7 (17.9)
IVd	4-ClC ₆ H ₄	4-BrC ₆ H ₄	169-70	D(aq)	7'	C ₂₀ H ₁₄ BrClN ₆ O ₃ S	45.3 (45.0)	2.5 (2.6)	15.9 (15.7)
IVe	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	210-11 (d)	E	74	C ₂₂ H ₂₀ N ₆ O ₃ S	58.7 (58.9)	4.6 (4.5)	18.5 (18.7)
IVf	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	201-2	E	77	C ₂₁ H ₁₇ BrN ₆ O ₃ S	48.9 (49.1)	3.5 (3.3)	16.6 (16.4)
Va	C ₆ H ₅	4-CH ₃ C ₆ H ₄	213-14	E	70	C ₂₁ H ₁₆ N ₆ O ₂ S	60.4 (60.6)	3.7 (3.8)	20.4 (20.2)
Vb	C ₆ H ₅	4-BrC ₆ H ₄	241-42	D + E	73	C ₂₀ H ₁₃ BrN ₆ O ₂ S	49.7 (49.9)	2.9 (2.7)	17.7 (17.5)
Vc	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	235(d)	D + E	69	C ₂₁ H ₁₅ ClN ₆ O ₂ S	56.2 (56.0)	3.5 (3.3)	18.5 (18.6)
Vd	4-ClC ₆ H ₄	4-BrC ₆ H ₄	229-30	E	74	C ₂₀ H ₁₂ BrClN ₆ O ₂ S	46.4 (46.6)	2.6 (2.3)	16.5 (16.3)
Ve	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	240(d)	D(aq)	67	C ₂₂ H ₁₈ N ₆ O ₂ S	61.6 (61.4)	4.3 (4.2)	19.4 (19.5)
Vf	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	274-75	E	72	C ₂₁ H ₁₅ BrN ₆ O ₂ S	50.7 (50.9)	2.9 (3.0)	17.1 (17.0)
VIa	C ₆ H ₅	4-CH ₃ C ₆ H ₄	159-60	B	56	C ₂₁ H ₁₆ N ₆ O ₃	62.9 (63.0)	4.1 (4.0)	20.8 (21.0)
VIb	C ₆ H ₅	4-BrC ₆ H ₄	227-28	B	59	C ₂₀ H ₁₃ BrN ₆ O ₃	51.8 (51.6)	3.0 (2.8)	17.8 (18.1)
VIc	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	209-10	B	64	C ₂₁ H ₁₅ ClN ₆ O ₃	57.8 (58.0)	3.3 (3.5)	19.5 (19.3)
VId	4-ClC ₆ H ₄	4-BrC ₆ H ₄	220(d)	B	60	C ₂₀ H ₁₂ BrClN ₆ O ₃	47.9 (48.1)	2.5 (2.4)	17.0 (16.8)
VIe	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	244(d)	B	62	C ₂₂ H ₁₈ N ₆ O ₃	63.5 (63.8)	4.5 (4.3)	20.0 (20.3)
VI f	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	228(d)	B	65	C ₂₁ H ₁₅ BrN ₆ O ₃	52.8 (52.6)	3.3 (3.1)	17.7 (17.5)
VIIa	C ₆ H ₅	4-CH ₃ C ₆ H ₄	157-58	B	68	C ₂₁ H ₁₆ N ₆ O ₂ S	60.7 (60.6)	4.0 (3.8)	20.0 (20.2)
VIIb	C ₆ H ₅	4-BrC ₆ H ₄	163-64	B	70	C ₂₀ H ₁₃ BrN ₆ O ₂ S	50.1 (49.9)	2.9 (2.7)	17.0 (17.2)
VIIc	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	220-21	B	72	C ₂₁ H ₁₅ ClN ₆ O ₂ S	56.2 (56.0)	3.5 (3.3)	18.5 (18.6)
VII d	4-ClC ₆ H ₄	4-BrC ₆ H ₄	159-60	B + P	74	C ₂₀ H ₁₂ BrClN ₆ O ₂ S	46.5 (46.6)	2.5 (2.3)	16.4 (16.3)
VIIe	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	215-16	B	66	C ₂₂ H ₁₈ N ₆ O ₂ S	61.6 (61.4)	4.0 (4.2)	19.7 (19.5)
VII f	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	145(d)	B + P	69	C ₂₁ H ₁₅ BrN ₆ O ₂ S	51.1 (50.9)	2.8 (3.0)	17.2 (17.0)
VIIIa	C ₆ H ₅		213(d)	E	65	C ₁₄ H ₉ N ₅ O ₃ S	51.6 (51.4)	3.0 (2.8)	21.2 (21.4)
VIIIb	4-ClC ₆ H ₄		232(d)	E	68	C ₁₄ H ₈ ClN ₅ O ₃ S	46.3 (46.5)	2.5 (2.2)	19.6 (19.4)
VIIIc	4-CH ₃ C ₆ H ₄		229(d)	E	66	C ₁₅ H ₁₁ N ₅ O ₃ S	52.9 (52.8)	3.5 (3.2)	20.3 (20.5)

*B= Benzene; D = Dioxane; E = Ethanol; M = Methanol; P = Pet.ether.

method, 0.1 ml of the drug solution (200 μ g in DMF) in 5 ml of sterilized fungi medium was treated with 3–4 drops of 48 hr old culture in a test tube. The test tubes were then shaken well and incubated for 48 hr at 37°. The extent of inhibition was determined by measuring the decrease in turbidity in terms of % transmission at 660 μ . The results of antibacterial and antifungal studies are given in Table 2 along with the results obtained for standards, sulfanilamide and phenol for antibacterial activity and salicylic acid for antifungal activity.

in vitro antitubercular testing against the human virulent H₃₇-RV strain of *Mycobacterium tuberculosis* by the method of disperse culture technique as described by Rake *et al.*¹⁸ The testing was conducted at different concentrations of drug solution in DMF using Kirchner's medium. The lowest concentration which showed no visible growth at the end of the incubation period was taken as the end point and it was observed that compounds IIIb, IVd, VIa and VIIc were active at 200 μ g/ml concentration whereas Ve was active at 100 μ g/ml. Under similar conditions, standards INH and PAS inhibited the growth at 0.4 μ g/ml.

Further, selected five compounds were subjected to .

Table 2—Antibacterial and Antifungal Activities of the compounds III–VIII

Compd	Antibacterial activity*				Antifungal activity*		
	E.C.	P.V.	K.P.	S.A.	A.N.	C.A.	A.F.
IIIa	++	—	—	++	++	++	++
IIIb	+	—	+	++	+	++	++
IIIc	+	+	+	+	++	+++	++
IVa	+	—	+	+	+	++	++
IVb	—	+	—	—	+	++	+
IVc	—	+	—	+	++	+++	++
IVd	+	+	+	+	+	+	++
IVe	+	—	+	+	++	+++	+
IVf	+	+	+	+	+	+	++
Va	+	+	—	++	+	+	+
Vb	+	++++	+	+	+	+	+
Vc	+	+	—	++	+	+	+
Vd	+	+	+	+	—	+	+
Ve	—	+	+	++	+	+	+
Vf	+	+	—	+	++	+++	++
VIa	+	++	+	+++	++	++	++
VIb	+	+	—	+	++	+++	+++
VIc	+	++	+	++	+++	+++	++
VId	+	+	+	—	++	++	++
VIe	+	+	—	—	++	++	++
VI f	+	++	+	+	++	++	++
VIIa	+	++	+	+++	++	++	+
VIIb	+	++	+	++	++	++	++
VIIc	+	+	+	++	++	+++	++
VII d	+	++	+	—	++	+++	+
VIIe	—	++	+	++	+	+++	+
VII f	+	—	—	++	+++	+++	+
VIIIa	+	—	++	+	++	+++	++
VIIIb	—	—	+	++	++	+++	++
VIIIc	++	—	+	—	+++	+++	+
S-1	+	++	+	+	+	+	+
S-2	+	++	—	+	+++	+++	+++
S-3							

*E.C. = *Escherichia coli*; P.V. = *Proteus vulgaris*; K.P. = *Klebsiella pneumoniae*; S.A. = *Staphylococcus aureus*; A.N. = *Aspergillus niger*; C.A. = *Candida albicans*; A.F. = *Aspergillus flavus*.
S-1 = Sulfanilamide; S-2 = Phenol; S-3 = Salicylic acid.

Antibacterial activity : Zone of inhibition in mm 14–16 = '—' (no activity); 17–19 = '+' (positive activity); 20–22 = '++' (positive activity); 23–25 = '+++ ' (positive activity); 26–28 = '++++' (positive activity); Antifungal activity : Percent transmission 1–25 = '—' (no activity); 26–50 = '+' (positive activity); 51–75 = '++' (positive activity); 76–100 = '+++ ' (positive activity). Solvent control : DMF

From the results obtained, the following observations could be made: Amongst the various compounds tested, only Vb, VIa, VIc, VIIa and VIIb exhibited antibacterial activity of high order. Rest of the compounds showed either moderate or no activity compared to that of standard. It is observed that cyclisation of thiosemicarbazides (IVa-f) to the corresponding 1,3,4-thiadiazoles (Va-f) appears to confer increased antibacterial activity and especially the compound Vb is highly active against *P. vulgaris*. The same trend of enhanced activity has been observed in cyclisation of the thiosemicarbazides (IVa-f) to 1,3,4-oxadiazoles (VIa-f) and 1,2,4-triazoles (VIIa-f). The compounds VIa and VIIa are found to be very active against *S. aureus*. It is noticed that introduction of 4-CH₃C₆H₄NH group at position-2 of 1,3,4-thiadiazole moiety enhances the activity considerably. Most of the 1,2,4-triazoles (VIIa-f) show better activity against *S. aureus*.

The results of antifungal screening reveal that cyclisation of thiosemicarbazides (IVa-f) to the corresponding 1,3,4-oxadiazoles (VIa-f) and 1,2,4-triazoles (VIIa-f) increase the activity appreciably. It is also observed that the conversion of acid hydrazides (IIIa-c) to 1, 3, 4-oxadiazoles (VIIIa-c) results in enhanced activity. Amongst the various compounds tested, compounds VIc, VIIf and VIIIc are highly active against *A. niger* and VIb is very active against *A. flavus*. It is interesting to note that most of the compounds, viz. IIc, IVc, IVe, Vf, VIc, VIId-f and VIIIa-c display significant antifungal activity against *C. albicans*. It can be concluded that introduction of 4-ClC₆H₄ group at position-3 of isoxazolo [5,4-d]-pyrimidine moiety increases the activity in most of the cases.

Only 5-[(3'-*p*-tolyl)isoxazolo [5,4-d]pyrimidin-4'-yl)-oxymethyl]-2-(*p*-toluidino)-1,3,4-thiadiazole (Ve) shows better antitubercular activity when compared to that of other series. In general, the compounds do not exhibit significant activity compared to the activity of standard drugs.

Experimental Procedure

M.p.s were determined in open capillaries and are uncorrected. IR spectra in nujol were recorded on Perkin-Elmer 221 and Perkin-Elmer 1378 spectrophotometers ($\nu_{\max}$ in cm⁻¹), PMR spectra in DMSO-*d*₆ on a Varian EM-390, 90 MHz spectrometer using TMS as internal standard (chemical shift in δ , ppm), and mass spectra on a Finnigan 4121 GC mass spectrometer at 70eV (low resolution). All the compounds were routinely checked for their structures by IR spectrometry, but the data have been presented only for representative compounds in the series.

Ethyl (3-substituted isoxazolo [5,4 d]pyrimidin-4-yloxy) acetates (IIa-c; Table 1)

A mixture of 0.1 mol of 4-hydroxy-3-substituted-isoxazolo [5,4 d]pyrimidine and 0.15 mol (20.7 g) of anhyd. K₂CO₃ in an excess of super dry acetone (375 ml) was stirred at reflux temperature for 3 hr. To the stirred suspension 12.25g (0.1 mol) of ethyl chloroacetate in dry acetone (50 ml) was added dropwise during 1 hr at reflux temperature and the refluxing continued for 8 hr. After keeping the reaction mixture overnight, the excess of solvent was removed and the residue poured onto crushed ice. The separated white solid was filtered, washed with water and recrystallised from ethanol; IR of IIa: 3049 (C-H), 1724 (ester C=O), 1681 (pyrimidine)²², 1587, 1538 (C=C); PMR (DMSO-*d*₆) of IIa: 8.35 (s, 1H, 6-H), 7.6-7.3 (m, 5H, Ar-H), 4.65 (s, 2H, OCH₂), 4 (q, 2H, COOCH₂) and 1.2 (t, 3H, CH₃).

(3-Substituted isoxazolo [5,4-d]pyrimidin-4-yl-oxy) acetic acid hydrazides (IIIa-c; Table 1)

To a suspension of II (0.05 mol) in ethanol (150 ml) 3.0 g (0.06 mol) of 99% hydrazine hydrate was added and the reaction mixture refluxed for 1.5 hr. The resulting clear solution was concentrated to a small bulk *in vacuo*. The mass was then added to 200 g of crushed ice and water and the solid that separated was filtered, washed thoroughly with cold water, dried and recrystallized from an appropriate solvent; IR of IIIb: 3500-3300 (N-H), 3030 (C-H), 1653 (C=O), 1631 (pyrimidine), 1565, 1538 (C=C); PMR (DMSO-*d*₆) of IIIb: 8.65 (s, 1H, 6-H), 7.5-7.0 (m, 5H, Ar-H), 6.8-6.1 (br, 3H, NHNH₂) and 3.6 (s, 2H, OCH₂).

*N*¹-(3'-Substituted isoxazolo [5, 4-d]pyrimidin-4'-yl-oxyacetyl)-*N*⁴-(*p*-substituted phenyl)-3-thiosemicarbazides (IVa-f; Table 1)

A mixture of III (0.01 mol) and 4-substituted-phenyl isothiocyanate (0.01 mol) in 150 ml of 90% ethanol was heated on a water-bath for 2 hr. The solid, obtained after subsequent concentration and cooling, was filtered, washed with ethanol, dried and recrystallised from a suitable solvent; IR of IVa: 3400-3000 (N-H), 3060 (C-H), 1695 (C=O), 1639 (pyrimidine), 1600, 1538 (C=C), 1220 (C=S).

5-[(3'-Substituted-isoxazolo [5,4-d]pyrimidin-4'yl)oxymethyl]-2-(p-substituted phenylamino)-1,3,4-thiadiazoles (Va-f; Table 1)

The appropriate thiosemicarbazide (IV; 0.01 mol) was added gradually, with stirring, to anhyd. orthophosphoric acid (20 ml) at 120° during 20 min. The reaction mixture was heated with stirring at 120° for another 30 min, cooled, poured into 300 g of crushed

ice and water with stirring, and allowed to stand overnight. The precipitated mass was filtered, washed with water, dried and crystallised from a suitable solvent; IR of Va : 3300 (N—H), 3030 (C—H), 1629 (pyrimidine), 1600, 1538, (C=C); PMR (DMSO-*d*₆) of Va : 9.65 (*s*, 1H, NH), 7.7 (*s*, 1H, 6'-H), 7.3–6.6 (*m*, 9H Ar-H), 4.2 (*s*, 2H, OCH₂) and 2.05 (*s*, 3H, CH₃); MS : *m/z* 416 (M⁺), 77 (C₆H₅⁺, base peak).

5-[(3'-Substituted-isoxazolo [5,4-d]pyrimidin-4'-yl)oxymethyl]-2-(p-substituted phenylamino)-1,3,4-oxadiazoles (VIa-f; Table 1)

A suspension of IV (0.01 mol) in ethanol (30 ml) was dissolved in cold aq. NaOH (5 ml, 4*N*) at 0°. To this clear solution, iodine in aq. KI (5%) was added gradually with stirring till the colour of iodine persisted at room temperature. The reaction mixture was heated under reflux for 2 hr, cooled and poured into ice water. The precipitated solid was filtered, washed with water and chromatographed on neutral alumina using benzene as eluant to get the pure compound; IR of VIa : 3340–3250 (N—H), 3070 (C—H), 1642 (pyrimidine), 1618, 1567 (C=C); PMR (DMSO-*d*₆) of VIa : 8.65 (*s*, 1H, NH), 7.85 (*s*, 1H, 6'-H), 7.5–6.6 (*m*, 9H, Ar-H), 4.15 (*s*, 2H, OCH₂) and 1.8 (*s*, 3H, CH₃).

5-[(3'-Substituted-isoxazolo [5,4-d]pyrimidin-4'-yl)oxymethyl]-4-(p-substituted phenylamino)-1,3,4-oxadiazoles (VIa-f; Table 1)

The appropriate thiosemicarbazide (IV, 0.01 mol) was dissolved in aq. NaOH (33 ml, 4%) and refluxed gently for 1 hr. The resulting clear solution was treated with decolourizing charcoal, cooled and filtered. The filtrate was adjusted to pH 5–6 with dil. acetic acid and the precipitated white solid filtered off after cooling. It was washed with water, dried and recrystallised from a suitable solvent; IR of VIIa: 3380 (N—H) 3030 (C—H), 1630 (pyrimidine), 1580, 1530 (C=C), 1180 (C=S); PMR (DMSO-*d*₆) of VIIa : 8.9 (*s*, 1H, NH), 7.6 (*s*, 1H, 6'-H), 7.2–6.6 (*m*, 9H, Ar-H), 3.8 (*s*, 2H, OCH₂) and 2.05 (*s*, 3H, CH₃).

3-[(3'-Substituted isoxazolo [5,4-d]pyrimidin-4'-yl)oxymethyl]-2-mercapto-1,3,4-oxadiazoles (VIIIa-c; Table 1)

A mixture of III (0.01 mol), 0.05*N* KOH solution (2 ml) and carbon disulphide (1 ml) in 50 ml of 95%

ethanol was refluxed on a water-bath for 6 hr. The solvent was evaporated and the residue dissolved in cold water. The resulting clear solution was acidified with dil. acetic acid to precipitate VIII which was filtered, washed with water, dried and recrystallized from ethanol: IR OF VIIIa : 3378 (N—H), 3060 (C—H), 1640 (pyrimidine), 1608, 1535 (C=C), 1183 (C=S); PMR (DMSO-*d*₆) of VIIIa : 9.45 (*s*, 1H, NH), 8.75 (*s*, 1H, 6'-H) 8–7.6 (*m*, 5H, Ar-H) and 4.5 (*s*, 2H, OCH₂).

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Reaction of 3-Hydrazino-5, 6-diphenyl-1, 2, 4-triazine with Unsymmetrical 1, 3-Bicarbonyl Compounds : Synthesis of Some New 3-(3', 5'-Disubstituted pyrazol-1'-yl)-5, 6-diphenyl-1, 2, 4-triazines & Their Antimicrobial Activity

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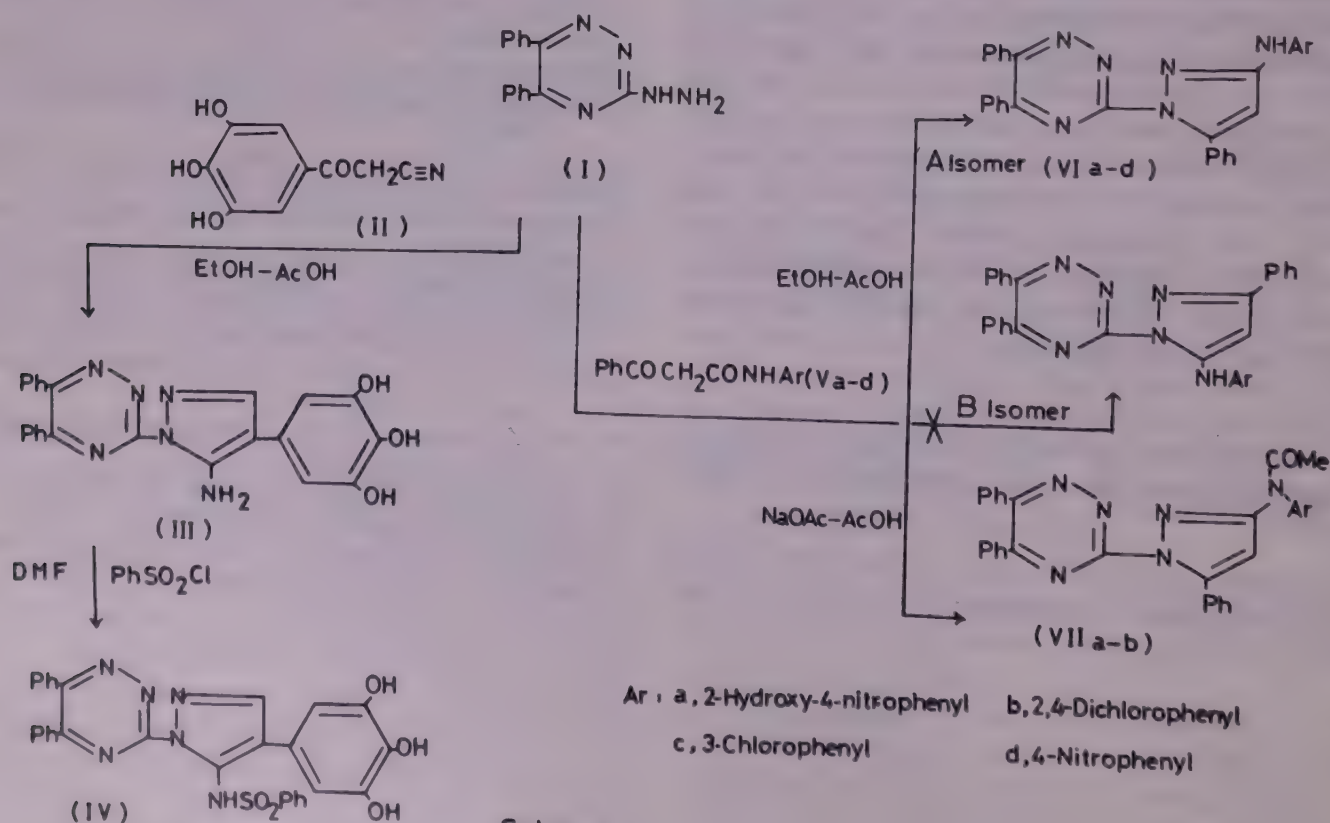
The reactions of 3-hydrazino-5, 6-diphenyl-1, 2, 4-triazine (I) with unsymmetrical 1, 3-bicarbonyl compounds such as α -cyanoacetophenone, benzoylacetanilide, anilino- α , β -unsaturated ketone, benzoylactic acid hydrazide, N¹-cyanoacetyl-N²-benzoylacetylhydrazine, N¹-benzene-N²-benzoyl-acetylhydrazine, 1, 1, 1-trifluoroacetylacetone, 1, 1, 1, 5, 5, 5-hexafluoropenta-2, 4-dione and 1 benzoylacetone-2-oxime, have been studied in abs. ethanol, gl. acetic acid and ethanol-piperidine media. These reactions result in some new 3-(3'-5'-disubstituted pyrazol-1'-yl)-5, 6-diphenyl-1, 2, 4-triazines. Some of these compounds show moderate antimicrobial activity.

In continuation of the earlier work¹⁻⁴ on 5, 6-diphenyl-1, 2, 4-triazine derivatives, the author reports herein the synthesis of new 3, 5-disubstituted pyrazoles containing a 5, 6-diphenyl-1, 2, 4-triazine moiety with a view to evaluating their antimicrobial activity.

3-Hydrazino-5, 6-diphenyl-1, 2, 4-triazine (I) when refluxed with α -cyanoacetophenone derivatives (II) in the presence of ethanol-acetic acid⁵ gave 3-[5'-amino-4'-(3'', 4'', 5''-trihydroxyphenyl)pyrazol-1'-yl]-5, 6-diphenyl-1, 2, 4-triazine (III), which on treatment with benzenesulphonyl chloride in dimethyl formamide

gave the benzenesulphonamide derivative (IV) (Scheme 1).

Hydrazino compounds on reaction with unsymmetrical 1, 3-bicarbonyl compounds (Va-d) should give the isomeric pyrazole derivatives A and B. However, only the A isomer was isolated in good yield due to the direction of enolization of 1, 3-diketones being towards aryl group⁶. Thus, cyclocondensation of I with benzoylacetamide derivatives (Va-d) in the presence of abs. ethanol produced 3-anilino-5-phenylpyrazole derivatives (VIa-d). A similar treatment of I with Va, b in the presence of gl. acetic acid-sodium



Scheme 1

acetate led to the formation of N-acylated pyrazole derivatives VIIa and VIIb respectively (Scheme 1).

Treatment of I with anilido- α, β -unsaturated ketones (VIIIa-d) in the presence of ethanol-piperidine⁷ resulted in the formation of monohydrazone (XIa-d) and/or 1-(5'-6'-diphenyl-1', 2', 4'-triazin-3'-yl)-3-phenyl-4-anilido-5-(2, 4-dichlorophenyl)pyrazolines Xa-d. Heating of IXa-d with ethanol-piperidine gave the pyrazoline derivatives Xa-d (m.p. and m.m.p. gave no depression). The probable mechanisms for these reactions are shown in Scheme 2.

Condensation of 3-hydrazino-5, 6-diphenyl-1, 2, 4-triazine (I) with benzoylacetic acid hydrazide (XI) in abs. ethanol gave the corresponding hydrazone XII, which underwent cyclization by heating with gl. acetic acid-sodium acetate to get XIII. Alkylation of XIII using ethyl bromoacetate in ethanolic KOH⁸ led to the formation of 1-aryl-[1, 2, 4]triazin[4, 3-b]pyrazolin-5-one derivatives (XIV) (Scheme 2).

Cyclocondensation of I with N¹-Cyanoacetyl-N²-benzoylacetylhydrazine (XVa) and N¹-benzoyl-N²-benzoylacetylhydrazine (XVb) in abs. ethanol yielded 3-(3'-cyanoacetic acid hydrazido-5'-phenylpyrazol-1'-yl)-5, 6-diphenyl-1, 2, 4-triazines (XVIa, b). Compound XVIa when heated with gl. acetic acid in the presence of sodium acetate afforded 3-cyanomethyl-1, 2, 4-triazolo[4,5-b]pyrazole derivative (XVII), while refluxing of XVIa with dil. hydrochloric acid gave the isolated heterotricyclic compound XVIII (Scheme 3).

The triazine (I) also underwent condensation with 1, 1, 1-trifluoroacetyl acetone and 1, 1, 1, 5, 5, 5-hexafluoropenta-2, 4-dione in abs. ethanol to give the corresponding 1, 3, 5-trisubstituted pyrazole derivatives (XIXa, b).

The action of 1-benzoylaceton-2-oxime (XX), prepared by heating benzoylaceton (in abs. ethanol) with $\text{NH}_2\text{OH} \cdot \text{HCl}$ (in water) for 1 hr (m.p. 73-75°), on I in acetic acid⁹ resulted in the formation of 3-(3'-methyl-5'-phenylpyrazol-1'-yl)-5-6-diphenyl-1, 2, 4-triazine (XXI) (Scheme 3). Its structure was established by elemental analysis, spectral data and the preparation of an authentic sample¹ (m.p. and m.m.p. 230-32°).

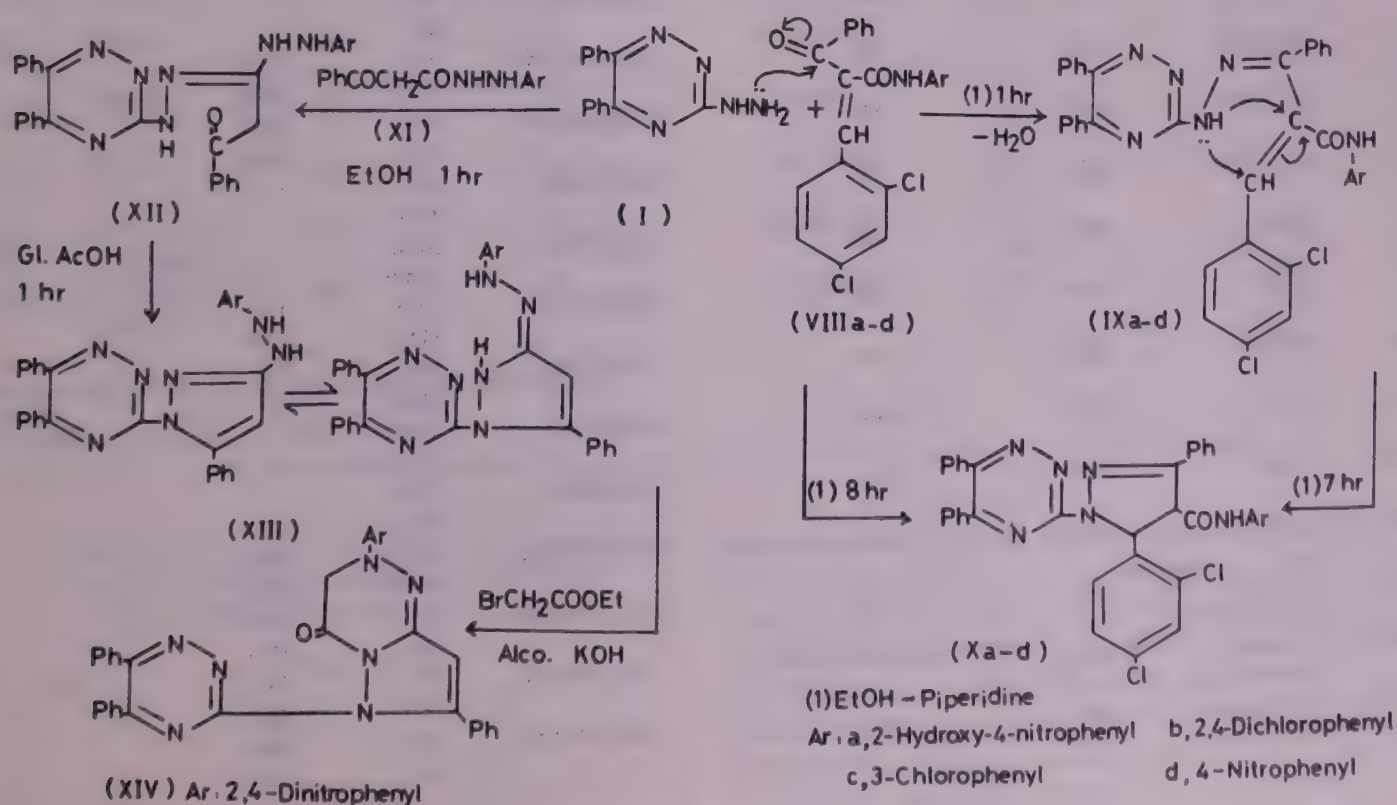
The characterization data of various compounds prepared are given in Table (1).

Antimicrobial Activity

The products and their parent substances were tested *in vitro* for their antimicrobial activity against a variety of bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris* and against the fungi such as *Aspergillus niger* and *Penicillium notatum*. All the compounds were inactive against the fungi except XXa, b and against the gram negative bacteria *Proteus vulgares*. The compounds XIX, XXa, b and XXII were more active against *Staphylococcus aureus*, *B. Subtilis* and *E coli* (Table 2).

Experimental Procedure

Melting points reported are uncorrected. UV sp-



Scheme 2

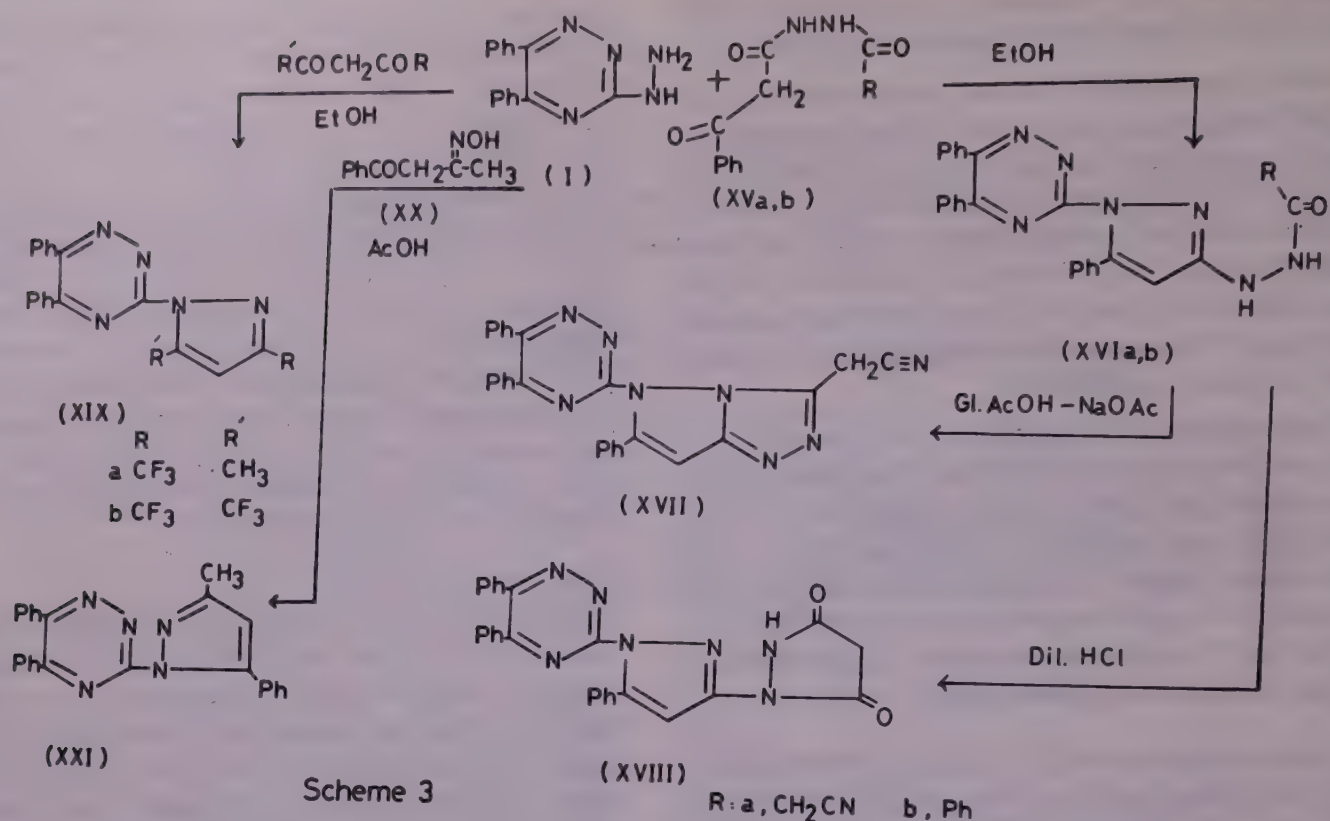


Table 1—Characterization Data of the Various Compounds Prepared

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)*		
					N	Cl	F
III	Dil. EtOH	275	65	C ₂₄ H ₁₈ N ₆ O ₃	19.0 (19.2)	—	—
IV	EtOH	115	70	C ₃₀ H ₂₂ N ₆ SO ₅ ⁺	14.5 (14.6)	—	—
Va	Dil. EtOH	195	90	C ₁₅ H ₁₂ N ₂ O ₅	9.1 (9.3)	—	—
Vb	Dil. EtOH	155	90	C ₁₅ H ₁₁ NCl ₂ O ₂	4.2 (4.5)	22.9	—
Vc	Dil. EtOH	145	85	C ₁₅ H ₁₂ NClO ₂	4.9 (5.1)	13.0	—
Vd	Dil. EtOH	255	75	C ₁₅ H ₁₂ N ₂ O ₄	9.6 (9.9)	—	—
VIa	EtOH	204	70	C ₃₀ H ₂₁ N ₇ O ₃	18.2 (18.6)	—	—
VIb	EtOH	210	75	C ₃₀ H ₂₀ N ₆ Cl ₂	15.5 (15.7)	13.5	—
VIc	EtOH	220	74	C ₃₀ H ₂₁ N ₆ Cl	16.7 (16.8)	7.0	—
VId	EtOH	245	80	C ₃₀ H ₂₁ N ₇ O ₂	19.0 (10.2)	7.2	—
VIIa	AcOH	110	67	C ₃₂ H ₂₃ N ₇ O ₄	17.0 (17.2)	—	—
VIIb	AcOH	105	65	C ₃₂ H ₂₂ N ₆ Cl ₂ O	14.2 (14.6)	12.1	—
VIIIa	pet. ether: MeOH (1:4)	260	60	C ₂₂ H ₁₉ N ₃ Cl ₃ O ₃	5.9 (6.1)	12.3	—
VIIIb	pet. ether: MeOH (1:4)	145	70	C ₂₂ H ₁₄ NCl ₄ O ₂	2.7 (3.0)	15.5	—
VIIIc	pet. ether: MeOH (1:4)	165	70	C ₂₂ H ₁₄ NCl ₃ O ₂	3.0 (3.2)	30.1	—
						24.6	—
						24.8	—

(Contd.)

Table 1—Characterization Data of the Various Compounds Prepared —Contd

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)*		
					N	Cl	F
VIII d	pet. ether: MeOH (1:4)	180	70	C ₂₂ H ₁₄ N ₂ Cl ₂ O ₄	6.1 (6.3)	15.8 16.1	— (—)
IXa	Dil. EtOH	90	65	C ₃₇ H ₂₅ N ₇ Cl ₂ O ₄	13.6 (14.0)	9.6 10.1	— (—)
IXb	Dil. EtOH	225	70	C ₃₇ H ₂₄ N ₆ Cl ₄ O	11.7 (11.8)	19.1 20.0	— (—)
IXc	Dil. EtOH	80	60	C ₃₇ H ₂₅ N ₆ Cl ₃ O	12.0 (12.2)	15.2 15.6	— (—)
IXd	Dil. EtOH	100	70	C ₃₇ H ₂₅ N ₇ Cl ₂ O ₃	13.8 (14.3)	10.1 10.3	— (—)
Xa	EtOH	255	65	C ₃₇ H ₂₅ N ₇ Cl ₂ O ₄	13.7 (14.0)	10.0 10.1	— (—)
Xb	EtOH	265	75	C ₃₇ H ₂₅ N ₆ Cl ₄ O	11.67 (11.8)	19.7 20.0	— (—)
Xc	EtOH	250	60	C ₃₇ H ₂₅ N ₆ Cl ₃ O	12.1 (12.5)	15.5 15.8	— (—)
Xd	EtOH	264	70	C ₃₇ H ₂₅ N ₇ Cl ₂ O ₃	14.0 (14.3)	10.0 10.3	— (—)
XI	AcOH	212	90	C ₁₅ H ₁₂ N ₄ O ₆	16.0 (16.3)	— —	— (—)
XII	MeOH	201	70	C ₃₀ H ₂₃ N ₉ O ₅	20.9 (21.4)	— —	— (—)
XIII	EtOH	115	60	C ₃₀ H ₂₁ N ₉ O ₄	21.7 (22.1)	— —	— (—)
XIV	pet. ether. (100-120°)	128	65	C ₃₂ H ₂₁ N ₉ O ₅	20.3 (20.6)	— —	— (—)
XVa	EtOH	220	90	C ₁₂ H ₁₁ N ₃ O ₃	16.8 (17.1)	— —	— (—)
XVb	EtOH	225	70	C ₁₆ H ₁₄ N ₂ O ₃	9.6 (9.9)	— —	— (—)
XVIa	EtOH	140	80	C ₂₇ H ₂₀ N ₈ O	23.5 (23.7)	— —	— (—)
XVIb	EtOH	200	65	C ₃₁ H ₂₃ N ₇ O	19.0 (19.3)	— —	— (—)
XVII	AcOH	150	70	C ₂₇ H ₁₈ N ₈	24.7 (24.5)	— —	— (—)
XVIII	EtOH	100	55	C ₂₇ H ₁₉ N ₇ O ₂	20.5 (20.7)	— —	— (—)
XIXa	pet. ether (100-120°)	125	75	C ₂₀ H ₁₄ N ₅ F ₃	18.1 (18.4)	— —	14.7 15.0
XIXb	pet. ether (60-80°)	90	90	C ₂₀ H ₁₁ N ₅ F ₆	16.0 (16.1)	— —	25.9 26.2

*All the compounds gave satisfactory C and H analyses.

†Found: S, 5.3. Calc. S, 5.5%.

Table 2 — Antibacterial Activity of Compounds XIX, XXa,b and XXII

Compound	MIC(μg/ml)	
	<i>B. subtilis</i>	<i>E. Coli</i>
XIX	50.0	50.0
XXa	20.0	20.0
XXb	12.0	12.5
XXII	100.0	12.5

spectra were recorded in distilled ethanol on a Perkin-Elmer (Type 550S) UV-vis spectrophotometer ($\lambda_{\max}$ in nm), IR spectra in KBr on a Beckman IR 4-spectrophotometer ($\nu_{\max}$ in cm^{-1}), and 60 MHz PMR spectra in DMSO- d_6 on an EM 360 NMR spectrometer using TMS as internal standard (chemical shifts in δ , ppm). Substituted α -cyanoacetophenone was prepared by treating the substituted phenacyl bromide with KCN in the presence of acetic acid¹⁰ (m.p. 160°). Compound

I was prepared following the procedure described by Laakso *et al.*¹¹

Reaction of ethyl benzoylacetate with primary aromatic amines, 2, 4-dinitrophenylhydrazine, cyanoacetic acid hydrazide, benzoic acid hydrazide: Formation of the compounds Va-d, XI, XVa and XVb.

Ethyl benzoylacetate (0.015 mol) was heated at 110° and the appropriate amine, hydrazine or acid hydrazide (0.01 mol) added to it. The reaction mixture was warmed at 140-150° for 1 hr and allowed to cool when needles separated out. The precipitated product was filtered, washed with dil. HCl and crystallized from dil. ethanol to give V, XI, XVa or XVb (Table 1). IR(Va): 3480 (OH), 3300-3100 (NH), 3050 (aromatic-CH), 2900 (aliphatic CH), 1680 (CO-ph), 1630 (CO-NH), 1510 (*as*NO₂), 1340 (*s* NO₂) and 1440 (CH₂ def.), UV (Vc): 250 and 320; UV (Vd): 280; PMR (Vc): 4.3 (*s*, 2H, CH₂), 4.7 (*s*, 1H, =CH-), 6.1 (*s*, 1H, OH), 7.7 (*m*, 4H, ph-CO), 8.0 (*m*, 4H, ph-NH) and 14.4 (*s*, 1H, NH); PMR (Vd): 3.7 (*s*, 2H, CH₂), 4.1 (*s*, 1H, =CH-), 6.0 (*s*, 1H, OH), 6.9 (*m*, 4H, ph-CO), 7.7 (*m*, 4H, ph-NH), and 14.5 (*s*, 1H, NH). The OH and NH protons disappeared on shaking with D₂O.

Anilido- α , β -unsaturated ketones (VIIIa-d)

An equimolar (0.05 mol each) mixture of an aromatic aldehyde and V was fused for 15-20 min, and the reaction mixture cooled and digested with pet. ether (60-80°). The separated product was filtered off, washed with pet. ether (60-80°) and crystallized from methanol-pet. ether (1:4) to give VIII (Table 1); IR (VIIIa): 3420 (OH) 3300-3200 (NH), 3010 (aromatic-CH) 2850 (aliphatic-CH), 1690 (conjugated C=O), 1620 (-CO-NH), 1660 (olefinic C=C), 1510 (*as* NO₂), 1350 (*s*NO₂) and 1420 (CH₂ def.).

3-[5'-Amino-3'-(3'', 4''- 5''-trihydroxyphenyl)pyrazol-1'-yl]-5, 6-diphenyl-1, 2, 4-triazine (III)

A mixture of I (5 mmol) and substituted α -cyanoacetophenone (II) (5 mmol) was refluxed in ethanol (20 ml) containing acetic acid (3 ml). The reaction mixture was left overnight at room temperature and the separated solid filtered, washed with water and crystallized from dil. ethanol to give III (Table 1); IR: 3400 and 3200 (NH₂); UV: 195, 270 and 340 (amino-pyrazole derivatives)¹².

Preparation of benzenesulphonamide (IV)

A mixture of III (0.01 mol) and benzenesulphonyl chloride (0.01 mol) in DMF (50 ml) was heated under reflux for 15 min and diluted with cold water. The solid thus obtained was recrystallized to give IV (Table 1).

Condensation of I with Va-d : Formation of VIa-d

A mixture of I (0.01 mol) and the appropriate benzoylacetanilide derivative (Va-d) (0.01 mol) in abs. ethanol (50 ml) was heated under reflux for 5 hr, left overnight and diluted with cold water. The solid thus obtained was filtered and crystallized from an appropriate solvent to give VI (Table 1); IR (VIa): 3450-3200 (OH, NH), 3040 (aromatic CH), 1620 (C=N), 1570 (C=C) 1510 (*as*NO₂), 1360 (*s*NO₂) and 1250 (C-N); UV (VIa): 260-290.

Reaction of I with Va and Vb: Formation of VIIa and VIIb

An equimolar (0.01 mol each) mixture of I and Va or Vb and gl. acetic acid (100 ml) was heated under reflux for 5 hr. cooled, diluted with cold water and filtered. The solid obtained was recrystallized to give VIIa or VIIb (Table 1); IR (VIIb): 3050 (aromatic CH), 2950 (aliphatic CH), 1770 (C=O), 1600 (C=N) and 1480 (CH₂ def); PMR (VIIb): 2.3 (*s*, 3H, COCH₃), 6.8-8.0 (*m*, 19H, Ar-H and pyrazole C₄-H).

Condensation of I with anilido α , β -unsaturated ketones (VIIIa-d) : Formation of hydrazones (IXa-d)

A mixture of I (0.01 mol) and VIII (0.01 mol) in abs. ethanol (100 ml) was heated under reflux for 2 hr, cooled, diluted with water and filtered. The solid obtained was recrystallized to give IX (Table 1); IR, 3450-3150 (OH, NH bonded), 3020 (aromatic CH), 1650 (amide CO), 1600-1580 (C=C, C=N), 1520 (*as* NO₂), 1360 (*s* NO₂) and 1270 (C-N); UV: 260 and 320.

4-Anilido-5-(2', 4'-dichlorophenyl)-1-(5'', 6''-diphenyl-1'', 2'', 4''-triazin-3''-yl)-3-phenylpyrazolines (Xa-d):

(a) *Cyclization of the hydrazone IXa-d*-Compound IX (0.01 mol) in abs. ethanol (50 ml) and piperidine (0.5 ml) was refluxed for 6 hr. Then reaction mixture was concentrated, cooled and poured onto ice-HCl. The separated product was filtered, washed with water and crystallized to give X (Table 1).

(b) *Cycloaddition of I with VIIIa-b*-An equimolar mixture of I and VIII (0.005 mol each) in ethanol (30 ml) and piperidine (0.5 ml) was refluxed for 8 hr. Work up as above gave X, identical (m.p. and m.m.p.) with that obtained by method (a); IR: 3450-3250 (OH, NH) 3020 (aromatic CH), 1660 (amide CO), 1580 (C=N), 1520 (*as* NO₂), 1340 (*s* NO₂) and 1620 (C-N); UV: 195, 270 and 370.

Condensation of I with benzoylacetacetic acid hydrazide (XI): Formation of XII

A suspension of I (0.01 mol) in abs. ethanol (50 ml) and XI (0.01 mol) was heated under reflux for 1 hr,

cooled and diluted with water. The solid obtained was filtered and recrystallized to give XII (Table 1); IR : 3380-3200 (NH, NH-NH group), 3040 (aromatic CH), 2890 (aliphatic CH), 1660 (C=O), 1610-1590 (C=N), 1510 (ν NO₂), 1330 (δ NO₂) and 1440 (CH₂ def.).

Cyclization of XII: Formation of 3-arylhydrazino-1-(5', 6'-diphenyl-1', 2', 4'-triazin-3'-yl)-5-phenylpyrazole (XIII).

A mixture of XII (4 g) and anhyd. sodium acetate (5 g) in gl. acetic acid (100 ml) was refluxed for 2 hr, cooled and diluted with water. The solid obtained was filtered and crystallized to give XIII (Table 1).

Reaction of XIII with ethylbromoacetate ; Formation of 1-aryl-[1, 2, 4]triazino[4, 3-b]pyrazolin-5-ones (XIV)

An equimolar of XIII and ethyl bromacetate in ethanolic KOH (5%, 50 ml) was heated under reflux for 4 hr, diluted with water and filtered. The solid obtained was recrystallized to give XIV (Table 1); IR : 3050 (aromatic CH), 1680 (C=O), 1590 (C=N), 1520 (ν NO₂), 1350 (δ NO₂) and 1440 (CH₂ def.). UV: 255 and 325.

Synthesis of 3-acid hydrazido-1-(5', 6'-diphenyl-1', 2', 4'-triazin-3'-yl)-5-phenylpyrazoles (XVIa, b)

A mixture of I (0.01 mol) and 1, 2-disubstituted hydrazine (XVa, b) (0.01 mol) in ethanol (100 ml) was heated under reflux for 4hr, cooled, poured into cold water and filtered. The solid obtained on recrystallization gave XVIa or XVIb (Table 1).

Cyclization of XVIa: Formation of XVII

A mixture of XVIa (3 g) and anhyd. sodium acetate (5 g) in gl. acetic acid (100 ml) was refluxed for 4 hr, cooled and diluted with water. The solid obtained was filtered and recrystallized to give XVII (Table 1); IR: 3300-3100 (NH broad due to tautomerism-N=C-CH₂CN $\rightleftharpoons$ -NH-C'-CH₂CN), 3030 (aromatic CH), 2900 (aliphatic CH), 2299 (C $\equiv$ N), 1640-1590 (C=N, C=C) and 1500 (CH₂ def.); UV: 260 and 325; PMR: 1.8(s, 2H, CH₂), 6.0(s, 1H, pyrazole C₄-H) and 7.2(m, 15H, Ar-H).

Acid hydrolysis of XVIa: Formation of XVIII

A suspension of XVIa (2 g) in dil. HCl (20%, 50 ml) was heated under reflux for 5 hr, cooled, neutralized with aq. sodium carbonate and the resultant solid recrystallized to give XVIII which did not give a

positive test for acids (Table 1); IR: 3200 (NH), 3040 (aromatic CH), 2890 (aliphatic CH), 1700-1650 (1,3-dione), 1570 (C=N) and 1440 (CH₂ def.): UV: 255 and 340 nm.

Reaction of I with fluorinated acetylacetones : Formation of XIXa and XIXb

A mixture of I (0.01 mol) and 1, 1, 1-trifluoroacetylacetone or 1, 1, 1, 5, 5, 5-hexafluoropenta-2, 4-dione (0.01 mol) in abs. ethanol (50 ml) was heated under reflux for 1 hr, cooled, diluted with water, and the resultant solid filtered and recrystallized to give XIXa or XIXb (Table 1).

Action of 1-benzoylacetone-2-oxime (XX) on I: Formation of XXI

A suspension of I (0.01 mol) i gl. acetic acid (20 ml) and XX(0.01 mol) in distilled water (5 ml) was heated under reflux for 2 hr, and filtered while hot. The solid obtained on recrystallization gave XXI¹, m.p. and m.m.p. 183°.

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An Efficient Route for γ -Alkyl- γ -butyrolactones[†]

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An efficient route for γ -alkyl- γ -butyrolactones (**1**) involving iodolactonisation is described.

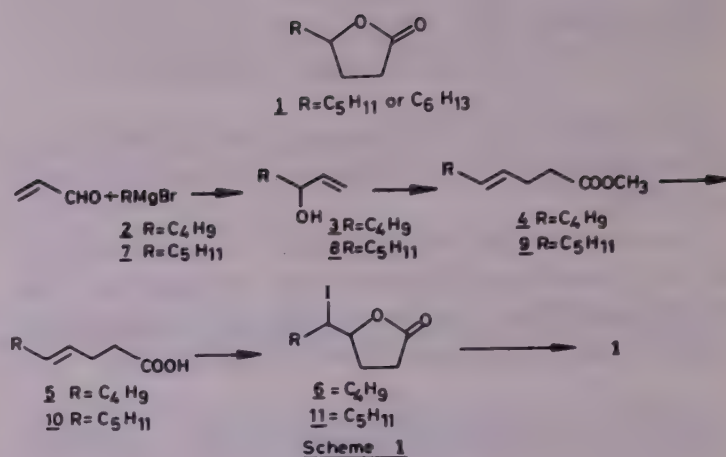
γ -Alkyl- γ -butyrolactones (**1**) are finding a great deal of importance in flavouring industries¹. In addition, some of these lactones are natural components of fruits and possess pheromone activity². Several methods have been reported to synthesise both chiral as well as racemic **1**^{3,4}. We now report a simple and efficient method for **1** ($R = C_5H_{11}$ or C_6H_{13}). The methodology adopted (see Scheme 1) involves cheap and readily available starting material and reagents and in fact can be applied for large scale preparations.

Thus, *n*-butylmagnesium bromide (**2**) and acrolein in ether at room temperature gave the corresponding allylic alcohol (**3**) in 80% yield⁵. Subsequent Claisen ortho-ester rearrangement⁶ of **3** with excess trimethyl orthoacetate and catalytic amount of propionic acid under reflux with constant removal of methanol gave **4** in 80% yield. Hydrolysis of **4** with methanolic potassium hydroxide gave the acid **5**. Treatment of **5** with iodine-potassium iodide in acetonitrile for 24 hr effected iodolactonisation⁶ to give **6** in 70% yield. **6** was stirred with excess of Raney nickel in ethanol for 24 hr to afford **1** ($R = C_5H_{11}$) in 95% yield. Compound **1** has been utilised as artificial coconut flavour in food industry.

Similarly, 5-hexyldihydro-2(3*H*)-furanose (**1**, $R = C_6H_{13}$), a component of apricot, plum and strawberry aromas, was synthesised by the same strategy via intermediates **7** → **11**.

Methyl 4*E*-nonenoate (**4**)

A mixture of **3**⁵ (36 g, 0.315 mol), trimethyl orthoacetate (60 g, 0.72 mol) and propionic acid (5 ml) was heated gradually at 100-105°, till no more methanol distilled off. Excess of trimethyl orthoacetate was removed *in vacuo*, the residue dissolved in ether, washed with brine, dried and concentrated. The residue was distilled under reduced pressure (b.p. 150-52°/20 mm) to afford **4** (46.5 g,



80%); PMR($CDCl_3$): δ 0.80 (*t*, 3H), 1-2.5 (*m*, 10H), 3.56 (*s*, 3H), 5.3 (*bs*, *m*); IR(neat): 1725 cm^{-1} .

4(*E*)-Nonenoic acid (**5**)

A solution of **4** (40 g, 0.22 mol) and 20% aq KOH (100 ml) in methanol (100 ml) was heated under reflux for 4 hr. Methanol was removed under reduced pressure, the residue acidified with 10% HCl, extracted with ether, washed with brine and dried. The removal of the solvent gave **5** (30.4 g, 90%). The crude acid was used for the next step (Found: C, 69.3; H, 10.4. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%).

γ -(1-Iodo-*n*-pentyl)- γ -butyrolactone (**6**)

To **5** (28.0 g, 0.176 mole) in acetonitrile (300 ml) was added iodine crystals (45.2 g, 0.176 mol) and potassium iodide (2 g) at 0°. After 24 hr at room temperature, solvent was removed under reduced pressure, the residue dissolved in ether and successively washed with aq. sodium thiosulfate, water and dried. The crude **6** (35.6 g, 70%) was used for further reaction without purification; PMR($CDCl_3$): δ 0.7-2.8 (*m*, 13H), 3.8-4.4 (*m*, 2H); IR(neat): 1730 cm^{-1} (Found: C, 38.3; H, 5.4. $C_9H_{15}IO_2$ requires C, 38.3; H, 5.3%).

5-Pentyldihydro-2(3*H*)-furanose (**1**, $R = C_5H_{11}$)

Compound **6** (27 g, 95 mmol) and Raney nickel (90 ml) in ethanol were stirred under hydrogen blanket for 24 hr. The reaction mixture was filtered and the filtrate concentrated. The crude product was distilled under reduced pressure to afford pure **1** ($R = C_5H_{11}$) (12.6 g, 85%), b.p. 150-52°/14 mm (lit b.p.³ 121°/6 mm); PMR: δ 0.8 (*t*, 3H), 0.9-2.6 (*m*, 12H), 4.37 (*m*, 1H).

[†] RRL-H Communication No. 2103

The authors thank Dr A V Rama Rao, Director, for his interest and guidance.

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Synthesis of 2-Formyl-6-hydroxymethyl-4-methyl-4,5,6,7-tetrahydrobenzo[b]furan: A Key Intermediate for Analogues of Homoprostacyclines†

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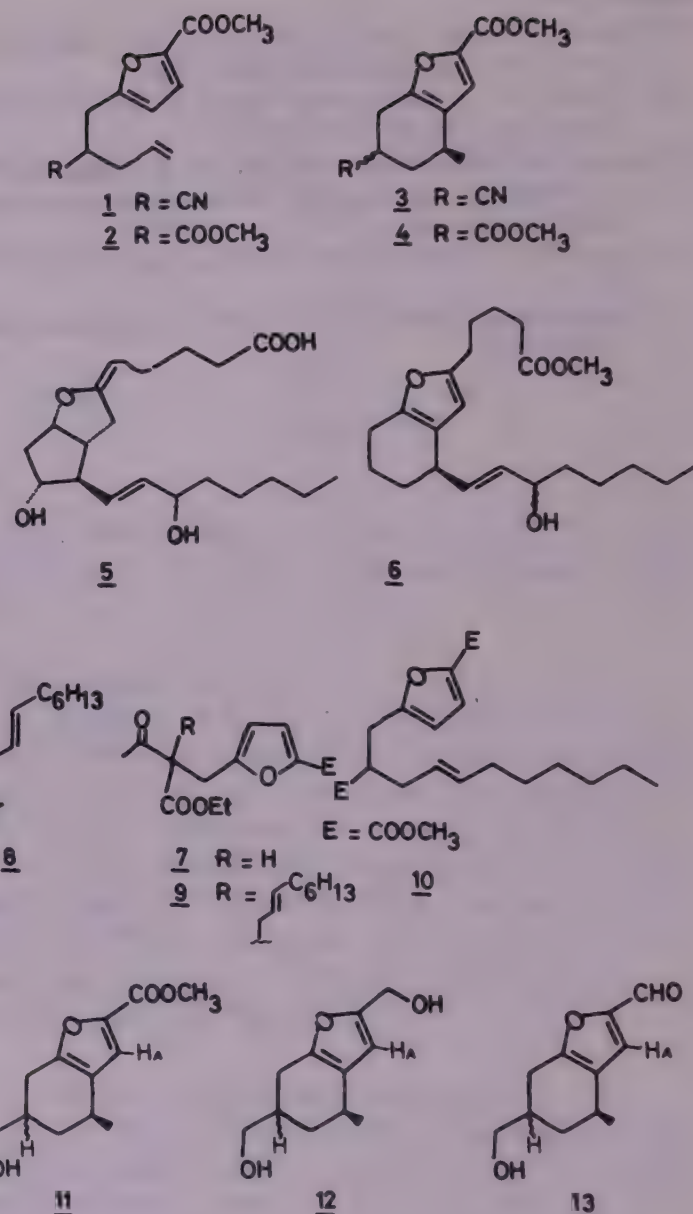
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2-Formyl-6-hydroxy-methyl-4-methyl-4, 5, 6, 7-tetrahydrobenzo[b]furan, a key Intermediate for homoprostacycline analogues, has been synthesized.

There is considerable interest in the synthesis of stable analogues of prostacyclines¹. In an earlier communication² we have reported stereoselective cyclisation of terminal olefins **1-4**. The structural similarity of **3** and **4** with the prostacycline **5**¹ suggests that these compounds could serve as suitable precursors for the synthesis of analogues of **5**. Our line of thinking has been recently vindicated by Richardson *et al.*,³ who have reported the synthesis of **6** on similar considerations. Preliminary screening by Chakravartty⁴ indicated that compound **4** showed CNS depressant activity. Encouraged by this finding, we first attempted to replace the methyl group at 4'-position by a suitable long chain.

Alkylation of **7**² with 1-bromo-2⁵-nonene (**8**)⁵ gave **9** in 62% yield. Deacylation followed by esterification with diazomethane yielded **10**. Attempts to cyclize the non-terminal olefin **10** using the procedure developed earlier in our laboratory for terminal olefins², did not yield any cyclised product as judged from the PMR spectrum. Attention was then directed towards modification of the ester moieties of **4**. Since the diastereoisomers were not separable by column chromatography, the mixture was used as such in the following transformations.

Diborane reduction of **4** using molar equivalence of tetra-*n*-butylammonium boronate according to the procedure of Brandström *et al.*,⁶ gave **11** in 63% yield. The absence of aliphatic -COOCH₃ peak at δ 3.73 and the presence of aromatic -COOCH₃ at 3.85 in the PMR spectrum confirmed the structure of this compound. The furanoproton (H_A) appeared at 7.05 indicating that the electron withdrawing ester group at



2-position of the furan ring was still present. Reduction of **4** with 0.5 molar equivalence of LAH yielded a mixture of **11** and **12**, which were easily separable by column chromatography. The structure of the compound **12** was easily confirmed by the total absence of ester peaks in the IR and PMR spectra and an upfield shift of the furano-proton to δ 6.13 in the PMR spectrum. However, a small peak for an aldehyde proton at δ 9.4 could not be eliminated even after repeated column chromatography. Reduction of **4** with two molar equivalence of LAH or SiO₃/LAH (procedure of Kamitori *et al.*)⁷ yielded the pure diol **12** uncontaminated by the aldehyde impurity. The diol **12** was not stable to vacuum distillation and rapidly turned brown even on storage in a refrigerator. Hence, this crude diol was subjected to chemoselective oxidation to the aldehyde **13** using BaMnO₄.⁸ This oxida-

†Part V of the series "Chemistry of Furans"

tion was difficult to follow by analytical TLC because **12** and **13** had similar R_f values. However, under the short wave-length UV light **12** showed up as a dark spot whereas **13** gave blue fluorescence. Total disappearance of the dark spot took 4 hr. Usual work-up procedures gave an oil in 67% yield. The appearance of -CHO proton at δ 9.44, the downfield shift of the H_A proton to 7.09 and one exchangeable proton in the methylene region at 1.51-2.97 for -OH group in the PMR spectrum confirmed the structure ¹³. The compound is a versatile key intermediate for the synthesis of analogues of homoprostacycline. Further work is in progress.

The financial assistance by DST, New Delhi through a scheme and a fellowship to one of us (B V) are gratefully acknowledged. One of the authors (TRV) wishes to thank CSIR, New Delhi for the award of a senior research fellowship.

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Convenient One-pot Synthesis of (Z)-4-Benzyloxy-2-buten-1-ol†

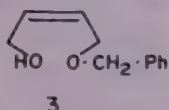
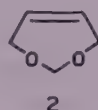
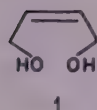
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Simple and one-step procedure for the preparation of (Z)-4-benzyloxy-2-buten-1-ol from (Z)-2-buten-1,4-diol is described.

4-Benzyloxy-2-buten-1-ol (**3**), a building block in organic synthesis¹⁻³, has attracted the attention as a prochiral synthon in natural product synthesis⁴⁻⁶ after the recent discovery of Sharpless asymmetric epoxidation⁷. In connection with our work on biologically active natural products, we required **3** (Z-isomer) in quantities. The reported method¹ for **3** consists of two steps, viz. (i) conversion of (Z)-2-buten-1-ol (**1**) into its benzylideneacetal (**2**) and (ii) reduction of **2** by lithium aluminium hydride - aluminium chloride¹ or by diisobutyl-aluminium hydride⁸.



We report herein a one-pot convenient synthesis of **3** in good yield. The potentiality of the method for large scale preparation of **3** is an added advantage. Hopefully, the method is also of general utility for the conversion of simple diols to their respective monobenzyl ethers⁹.

A mixture of **1** (17.6 g, 0.2 mol), benzyl bromide (17.1 g, 0.1 mol), anhydrous potassium carbonate (50 g), and potassium iodide (1 g) in dry acetone

(200 ml) was refluxed with vigorous stirring till all the benzyl bromide disappeared from the reaction mixture (36-40 hr, TLC). The reaction mixture was cooled, filtered through sintered funnel and most of the solvent was distilled off. The residue was dissolved in ether (100 ml), washed with water to remove excess of **1**, the organic layer dried (Na_2SO_4) and solvent evaporated. The residue was purified by column chromatography over silica gel to give **3** (14 g, 75%, calculated on benzyl bromide). Alternatively the residue was purified by fractional distillation under reduced pressure; b.p.⁸ 140-45°/1 mm Hg; PMR⁸ (CCl_4): δ 2.86 (m, 1H, exchangeable), 3.96 (m, 4H), 4.4 (s, 2H), 5.6 (m, 2H, olefinic) and 7.2 (s, 5H, aromatic).

Similarly were prepared $\text{Ph-CH}_2\text{-O-(CH}_2)_2\text{-OH}$, $\text{Ph-CH}_2\text{-O-(CH}_2)_2\text{-O-(CH}_2)_2\text{-OH}$ and $\text{CH}_2=\text{CH-CH}_2\text{-O-CH}_2\text{Ph}$. Satisfactory spectral data have

OH

been obtained for all these compounds.

We would like to thank Drs T Ravindranathan and A V Rama Rao for useful discussion.

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†NCL Communication No. 4133

Bridged Hydroquinolines

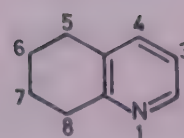
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The pyridannulation procedure of condensing vinamidinium salts with ketones having a free α -methylene has been adapted to prepare 3-substituted 5,6,7,8-tetrahydroquinolines; characterization data for the seven systems synthesized are reported. Conditions required are less drastic than those for recently reported alternative approaches to analogous systems. The adaptation has considerable generality even though 5, 8-methano-bridged 5,6,7,8-tetrahydroquinolines are not accessible through it. Chirality in the starting ketones, not affected by exposure to enolizing conditions, is preserved in the pyridannulated products.

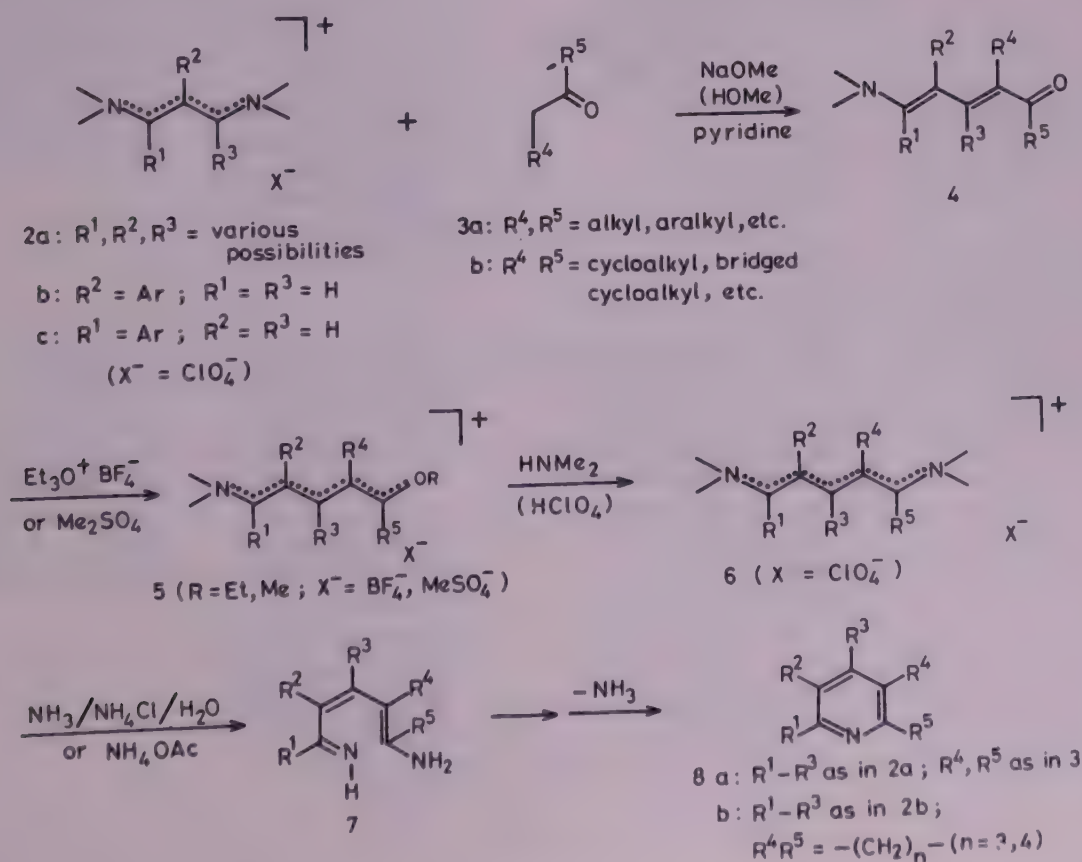
Recent communications by Chelucci *et al.*¹ describe synthetic strategies for various 5,6,7,8-tetrahydroquinolines (**1**), including those with 5,7-, 5,8- or 6,8-methano bridging. In comparison with the reaction conditions required in these strategies (heating reactants to 300°C in an autoclave), those pertinent to a general procedure for substituted pyridines developed earlier by Jutz² (Scheme 1) are quite mild and, by choice of suitable cyclic ketones (**3b**) and vinamidiniums (**2**), the procedure can be adapted to the syn-



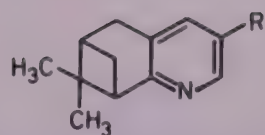
1 (with substitution at various positions and/or having 5,7-, 5,8- or 6,7-methano bridging)

thesis of various cycloalkeno-pyridines (with the possible exception of 6,8-methano bridged hydroquinolines; see below). We have reported earlier³ the preparation of 3-substituted-5,6-cycloalkenopyridines (**8b**), with cyclohexanone and cyclopentanone as the starting ketones and employing a somewhat shortened version of Scheme 1 (see below). Subsequent to that report, the shortened method was applied to prepare 5,8-methano bridged 3-substituted hydroquinolines (**9**), starting with nopinone⁴(**10**) as the ketone and the symmetric vinamidiniums⁵(**2b**) as the pyridannulating agents. Systems **9** were needed in a study that has now been completed⁶ and characterization data on those synthesized are gathered in Table 1; procedures followed were as already detailed³.

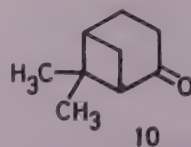
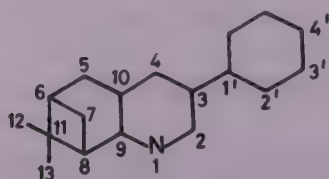
While the Jutz procedure, properly followed, should lead solely to the desired substituted pyri-



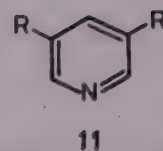
Scheme 1



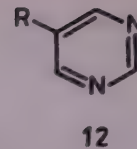
- 9a: R = H
 b: R = Cl
 c: R = C₆H₅
 d: R = p-MeOC₆H₄
 e: R = p-MeC₆H₄
 f: R = p-ClC₆H₄
 g: R = p-O₂NC₆H₄



10



11



12

R = R² as in 2b

dines, our shortened one-pot modification, by which we sought to convert the presumably formed intermediates, the vinylogous amides (4), directly into the pyridines (8) by the intervention of ammonia, yielded the required cycloalkenopyridines but admixed with side-products formed in independent, ammonia-induced reactions of (2). When the symmetric 2b are

employed, the side-products are the pyridines (11) (major) and the pyrimidines (12) (minor), formed in sizeable amounts (ca 30% of 2b converted; isolation of the desired hydroquinolines is effected, most conveniently, by centrifugal TLC). Cyclodimerization of systems 2b, with elimination from the initial cyclates, has been suggested³ as the pathway to 11. Discussion of modes of formation of 12, identified subsequent to the publication of reference 3, is deferred to in the context of reporting regioselectivities observed⁶ when the unsymmetric 2c are employed as the pyrid-annulating agents.

Any chirality present in ketones (3), not destroyed on exposure to enolizing conditions (e.g. R⁴ asymmetric), would continue to be present in the derived pyri-

Table 1—Characterization Data of Hydroquinolines (9)^a Prepared

Compd.	Yield (%) ^b	Picrate m.p. (°C)	Analytical data	NMR (δ; ex-TMS) ^c	
				¹ H	¹³ C
9a	40	182	Found: C, 83.4; H, 8.3; N, 7.82. C ₁₂ H ₁₅ N requires C, 83.19; H, 8.73; N, 8.08%.	8.22 (1H, d, br, H-2), 7.47-7 (2H, m, H-3 & H-4), 3.08-2.93 (3H, m, H-3 & H-5), 2.83-2.54 (1H, m, H-7a), 2.47-2.25 (1H, m, H-6), 1.42 (3H, s, H-12), 1.33-1.25 (3H, d, J=10Hz, H-7b), 0.65 (3H, s, H-13).	165.95 (C-9), 144.57 (C-2), 144.12 (C-10), 135.66 (C-4), 121.47 (C-3), 49.74 (C-8), 40.18 (C-6), 31.27 (C-5), 30.72 (C-7), 39.13 (C-11), 26.01 (C-12), 21.19 (C-13).
9b	35	178	Found: C, 69.46; H, 6.70; N, 6.92. C ₁₂ H ₁₄ NCl requires C, 69.39; H, 6.75; N, 6.89%.	8.01-7.98 (1H, d, J=6-7Hz, H-2), 7.31-7.27 (1H, d, J=6-7Hz, H-4), 3.55-3.53 (1H, t, J=4-5Hz, H-8), 3.08 (1H, br, H-5), 2.85-2.72 (1H, m, H-7a), 2.41-2.39 (1H, m, H-6), 1.45 (3H, s, H-12), 1.41-1.37 (1H, d, J=10Hz, H-7b), 0.68 (3H, s, H-13).	166.4 (C-9), 147.46 (C-2), 145.1 (C-10), 136.18 (C-4), 131.5 (C-3), 49.6 (C-8), 40.14 (C-6), 31.24 (C-5), 30.76 (C-7), 39.13 (C-11), 26.04 (C-12), 21.17 (C-13).

(Contd.)

Table 1—Characterization Data of Hydroquinolines (9)^a Prepared—Contd

Compd	Yield (%) ^b	Picrate m.p. (°C)	Analytical data	NMR (δ ; ex-TMS) ^c	
				¹ H	¹³ C
9c	65	202	Found: C, 86.62; H, 7.54; N, 5.72. C ₁₈ H ₁₉ N requires C, 86.7; H, 7.6; N, 5.6%.	8.45 (1H, d, J=2-3Hz, H-2), 7.66-7.36 [5H, m, 2x(H-2' & 3') & H-4], 3.06-3(3H, m, H-5 & H-8), 2.79-2.71 (1H, m, 7a), 2.39-2.3(1H, m, H-6), 1.44(3H, s, H-12), 1.41-1.25(1H, d, J=10Hz, H-7b), 0.7(3H, s, H-13).	165.1(C-9), 143.47(C-2), 138.21(C-10), $\longleftrightarrow$ 134.34(C-3), 129.81(C-1'), 128.77(C-2') $\longleftrightarrow$ 126.76(C-3'), 127.41(C-4'), 49.9(C-8), 40.11(C-6), 39.17(C-11), 30.73(C-7), 25.96(C-12), 21.13(C-13).
9d	48	208-210	Found: C, 81.5; H, 7.3; N, 5.3. C ₁₉ H ₂₁ NO requires C, 81.7; H, 7.5; N, 5%.	8.43(1H, d; J=2-3Hz, H-2), 7.58(1H, J=2-3Hz, H-4), 7.5-6.95 [4H, AA'BB' pattern 2x(H-2' & H-3')], 3.8(3H, s, H-14), 3.05-2.91(3H, m, H-5 & H-8), 2.76-2.68(1H, m, H-7a), 1.38-1.23(1H, d, J=10Hz, H-7b), 1.12(3H, s, H-12), 0.68(3H, s, H-13).	164.23(C-9), 159.2(C-4'), 142.71(C-2), 130.48(C-10) $\longleftrightarrow$ 134.06(C-3) $\longleftrightarrow$ 130.22(C-1'), 133.54(C-4), 127.82(C-3'), 114.2(C-2'), 49.59(C-8), 40.03(C-6), 39.18(C-11), 31.19(C-7), 30.73(C-5), 28.98(C-12), 21.17(C-13).
9e	55	195	Found: C, 86.82; H, 7.7; N, 5.15. C ₁₉ H ₂₁ N requires C, 86.7; H, 7.9; N, 5.3%.	8.85(1H, d, J=2-3Hz, H-2), 8.47(1H, d, J=2-3Hz, H-4), 7.62-7.24 [4H, AA'BB' pattern, 2x(H-2' & H-3')], 3.07-3.03(1H, m, H-8), 3-2.99(2H, d, J=2Hz, H-5), 2.78-2.7(1H, m, H-7a), 2.36-2.3(1H, m, H-6), 2.38(3H, s, H-14), 1.43(3H, s, H-12), 1.33-1.3(1H, d, J=10Hz, H-7b), 0.69(3H, s, H-13).	165.01(C-9), 143.6(C-2), 137.42(C-10) $\longleftrightarrow$ 135.66(C-3) $\longleftrightarrow$ 136.4(C-4'), 133.7(C-4), 129.2(C-1'), 129.72(C-2') $\longleftrightarrow$ 126.86(C-3'), 50.16(C-8), 40.48(C-6), 39.46(C-10), 31.46(C-7), 31(C-5), 26.19(C-12), 21.33(C-13), 21.08(C-14).
9f	42	216	Found: C, 76.25; H, 6.4; N, 4.85. C ₁₈ H ₁₈ NCl requires C, 76.1; H, 6.3; N, 4.9%	8.43(1H, d, J=2-3Hz, H-2), 7.6(1H, d, J=2-3Hz, H-4), 7.52-7.43 [4H, AA'BB'	165.61(C-9), 143.2(C-2), 139.58(C-10), 136.73(C-1'), 133.97(C-4') $\longleftrightarrow$ 130.23(C-3) $\longleftrightarrow$ 133.7(C-4), 129.09

(Contd.)

Table 1—Characterization Data of Hydroquinolines (9)^a Prepared—Contd

Compd.	Yield (%) ^b	Picrate m.p. (°C)	Analytical data	NMR (δ ; ex-TMS) ^c	
				¹ H	¹³ C
				pattern, 2x(H-2' & H-3')], 3.06-3.01(3H, m, H-8 & H-5), 2.79-2.71(1H, m, H-7a), 2.39-2.33(1H, m, H-6), 1.44(3H, s, H-12), 0.69(3H, s, H-13).	(C-3'), $\leftrightarrow$ 128.12 (C-2'), 49.84(C-8), 40.09(C-6), 39.33 (C-11), 31.31(C-5), 26.06(C-12), 21.29 (C-13).
9g	40		Found: C, 72.9; H, 6.25; N, 9.48. $C_{18}H_{18}N_2O_2$ requires C, 73.45; H, 6.1; N, 9.5%.	8.72(1H, d, J=2-3Hz, H-2'), 7.85(1H, d, J=2-3Hz, H-4), 8.33-7.4[4H, AA'BB' pattern, 2x(H-2' & H-3')], 3.04-2.88(3H, m, H-8 & H-5), 2.78-2.54(1H, m, H-7a), 2.29-2.15(1H, m, H-6), 1.39(3H, s, H-12), 1.35-1.1(1H, d, J=10Hz, 7b), 0.67(3H, s, H-13).	167.8(C-9), 145.2(C-2), 144.7(C-4'), 132.5(C-4), 130.9 (C-3'), 128.9(C-2'), 127.4(C-10), 124.3(C-1'), 49.4 (C-8), 40.3(C-6), 39.34(C-11), 29.42 (C-5), 26.28(C-12), 21.36(C-13).

^aExcepting 9g, which can be recrystallized from ethanol as reddish-brown needles (m.p. 51°), systems 9, all atmosphere—sensitive straw yellow oils, were purified by molecular transfer distillation under reduced pressure and stored in an inert atmosphere.

^bBased on nopinone (10)

^cCarbon numbering is as shown below:

Proton numbering follows carbon numbering.

^d $[\alpha]_D^{25}$ —57.25 (c 1.0, chloroform)

^e $[\alpha]_D^{25}$ —22.97 (c 0.37, chloroform)

dines (8) since neither Scheme 1 nor our modification thereof should affect such chirality. Nopinone (10) taken was optically active $\{[\alpha]_D^{20} + 18.6$ (neat); lit.⁴ $[\alpha]_D^{18} + 18.8\}$ and the product hydroquinolines (9) were expected to be optically active. Specific rotations of two of systems 9 tested are included in Table 1.

Camphor failed to react under our conditions. Such nonreactivity could be true, generally, of other ketones where conformational constraint, besides that of the type present in bicyclo[2.2.1]hept-2-ones, may inhibit free enolization. Thus 5,8-methanol bridged and certain other hydroquinolines may not be accessible through our method (cf reference 1b).

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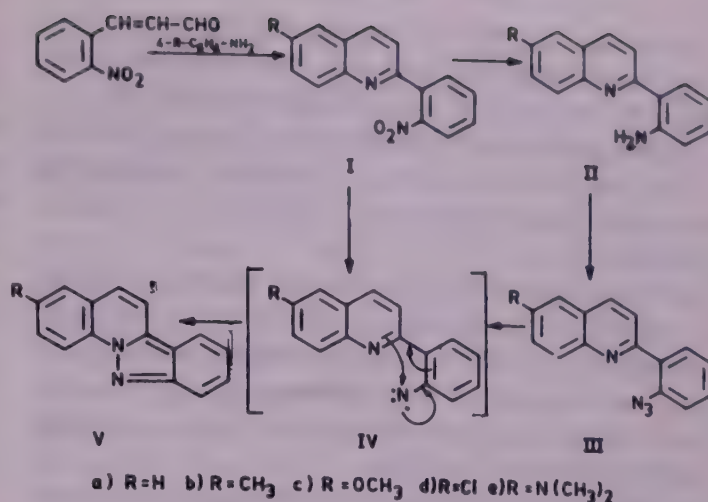
Synthesis of Indazolo[2, 3-*a*]quinolines

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A number of 2-(*o*-nitrophenyl)quinolines (Ia-e) have been synthesised and converted via amines (IIa-e) into corresponding azides (IIIa-e). Thermolysis and deoxygenation of 2-(*o*-azidophenyl)- (IIIa-e)- and 2-(*o*-nitrophenyl)-(Ia-e)-quinolines respectively lead to the formation of indazolo[2, 3-*a*]quinolines (Va-e).



Yamashita and coworkers¹ prepared indazolo[2,3-*a*]quinoline by the reaction of the quinolinium ylids with benzyne. In continuation of our work on *o*-substituted aryl azides²⁻⁵, we report a convenient synthesis of indazolo[2,3-*a*]quinolines (Va-e) from Ia-e.

It is observed that deoxygenation of 2-(*o*-nitrophenyl)quinoline (Ia) by triethyl phosphite as well as by ferrous oxalate affords Va. Further, thermolysis of 2-(*o*-azidophenyl)quinoline (IIIa) derived from Ia in decalin also yields Va.

2-(*o*-Nitrophenyl)quinolines (Ia-e) were prepared as follows: A mixture of *o*-nitrocinnamaldehyde (0.06 mol) and the aromatic amine (0.06 mol) was boiled in conc. HCl (30 ml) for 6 hr. The reaction mixture was neutralised, extracted with chloroform, the chloroform extract concentrated and the residue subjected to chromatography over a column of neutral alumina eluting Ia-e with 1:1 petroleum ether—benzene mixture (Table I).

2-(*o*-Azidophenyl)-6-substituted quinolines were prepared from Ia-e by reduction followed by diazotisation of the resulting amines (IIa-e) and treatment with sodium azide. Thus to a solution of I (0.025 mol) in methanol (40 ml) containing a pinch of Raney nickel, a solution of hydrazine hydrate (6 ml) in methanol was added, and the reaction mixture was allowed to stand at room temperature for 30 min with occasional shaking. The mixture was heated on a steam bath for 15 min, the catalyst was filtered and the filtrate chromatographed on a column of basic alumina eluting with petroleum ether to yield IIa-e.

A solution of II (0.02 mol) in 1.5 *N* HCl (30 ml) was diazotised at 0-5°. To this sodium azide (0.03 mol) was added in small portions and the reaction mixture was maintained at 0-5° for 1 hr. 2-(*o*-Azidophenyl)quinoline (III) that separated out was filtered and purified by chromatography over a column of neutral alumina eluting with petroleum ether.

Table I—Melting Points and Yields of I, II, III and V

Compd	R	I		II		III		V	
		m.p. °C	Yield %	m.p. °C	Yield %	m.p. °C	Yield %	m.p. °C	Yield %
a	H	123 (121) ⁶	25	153	80	153(d)	86	110 (107-109) ¹	80
b	-CH ₃	148	27	126	78	180(d)	88	144	75
c	-OCH ₃	130	27	155	84	118	80	160	75
d	-Cl	160	25	145	84	148(d)	90	163	71
e	-N(CH ₃) ₂	180	28	206	80	120	85	177	72

All the compounds analysed satisfactorily for C, H and N. PMR of IIIb (CDCl₃): δ 2.2 (s, 3H, CH₃), 7.1 to 8.8 (m, 9H, aromatic); IIIc (CDCl₃): δ 3.88 (s, 3H, OCH₃), 7.03 to 8.23 (m, 9H, aromatic); IIIe (CDCl₃): δ 3.03 [s, 6H, N(CH₃)₂], 7.01 to 8.25 (m, 9H, aromatic); Vb (CCl₄): δ 2.33 [s, 3H, CH₃], 6.9 to 8.63 (m, 9H, aromatic); Vc (DMSO-*d*₆): δ 3.93 (s, 3H, OCH₃), 7.2 to 8.8 (m, 9H, aromatic); and Ve (CDCl₃): δ 3.05 [s, 6H, N(CH₃)₂], 7.0 to 8.23 (m, 9H, aromatic).

Thermolysis of 2-(*o*-azidophenyl)quinolines (IIIa-e) was carried out as follows: A solution of III (0.005 mol) in decalin (40 ml) was heated to 160° for 30 min. Decalin was removed under reduced pressure and the residue chromatographed over a column of neutral alumina eluting pure Va-e with petroleum ether.

Deoxygenation of 2-(*o*-nitrophenyl)quinolines (Ia-e) was carried out either by treatment with triethyl phosphite (method-a) or with ferrous oxalate (method-b).

(a) A mixture of I (0.005 mol) and excess of triethyl phosphite was refluxed for 4 hr under nitrogen atmosphere. Excess triethyl phosphite was removed by a rapid stream of nitrogen at its b.p. The residue was subjected to chromatography to give pure V. The yields were about 70-75%.

(b) An intimate mixture of I (0.005 mol) and ferrous oxalate (0.02 mol) was heated around 250° for 1 hr. The reaction mixture was cooled, the solid was packed over the top of neutral alumina column and subjected to chromatography. The yields of V were about 45-50%.

The structures of the intermediates (I-III) and products (V) were adequately supported by elemental analyses, IR PMR spectral data. Their m.ps. and yields are given in Table I. A nitrene intermediate (IV) may be suggested in the thermolysis and deoxygenation respectively of III and I. No products expected as a result of H-abstraction, C-H insertion and dimerisation of the nitrene intermediate (IV) such as amino and azo compounds were isolated in these reactions indicating that singlet nitrene is involved.

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Studies in Heterocyclisation of Michael Products from Isoxazoles

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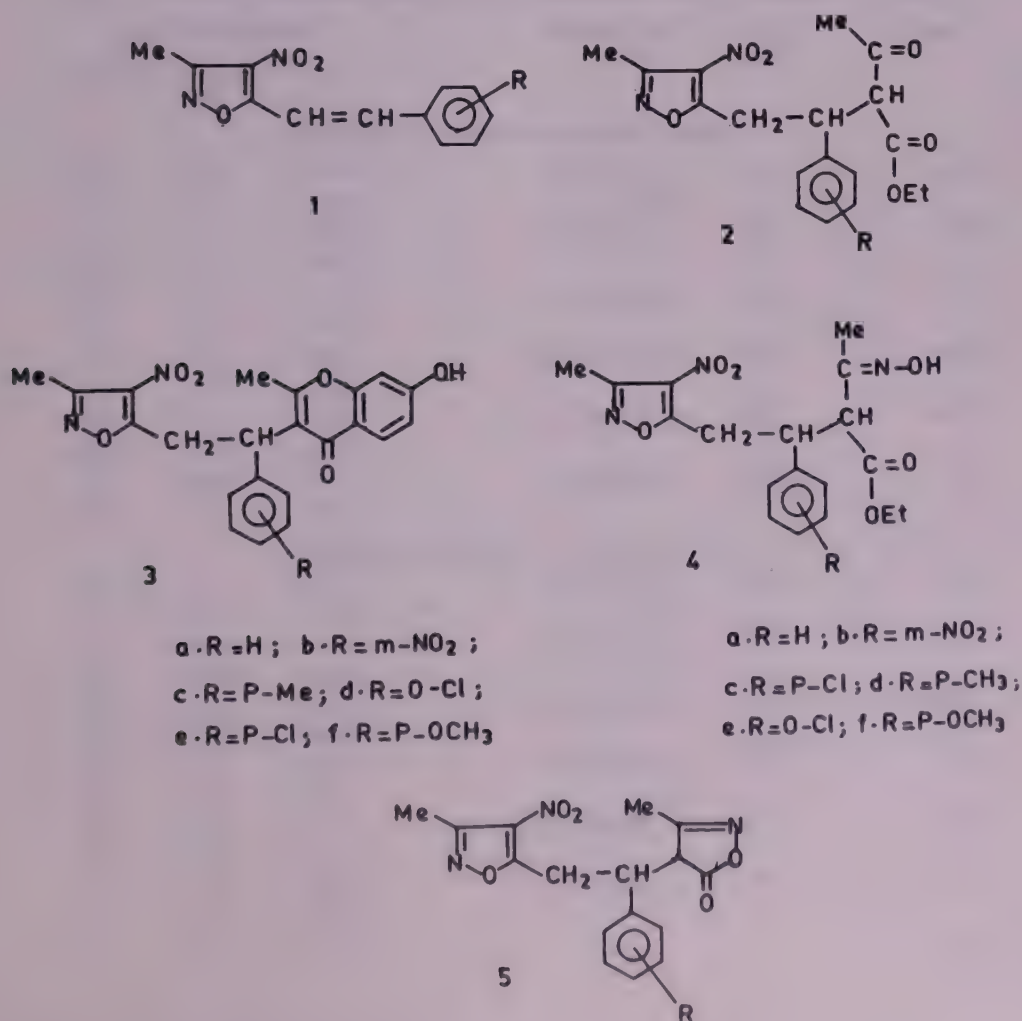
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The Michael adducts (**2a-f**) obtained by the interaction of 3-methyl-4-nitro-5-styrylisoxazoles (**1**) and ethyl acetoacetate have been treated with resorcinol and hydroxylamine separately. With resorcinol the chromones (**3a-f**) are obtained whereas with hydroxylamine open chain oximes (**4a-f**) are the products.

Michael addition to 4-nitroisoxazoles and utilization of the resulting ε -nitroketones in a variety of heterocyclic synthesis, such as azepines¹, isoxazoles² and pyrazoles^{3,4} have been reported from our laboratory. In continuation of our interest in the same direction herein we report the interaction of β -dicarbonyl compounds derived from nitroisoxazole with resorcinol and hydroxylamine.

3-Methyl-4-nitro-5-styrylisoxazoles² (**1**) were prepared from acetylacetone by a sequence of processes involving cyclization with NH_2OH , nitration and regiospecific styrylation under Knoevenagel conditions. Addition of ethyl acetoacetate to **1** led to ethyl 2-[1-phenyl-2-(3-methyl-4-nitro-5-isoxazolyl)-ethyl] acetoacetates (**2**) in 60-70% yields. Compounds **2** and resorcinol under Pechmann conditions resulted in a chromone rather than a coumarin as revealed by the appearance of $\nu \text{C}=\text{O}$ at 1670cm^{-1} ; in the case of coumarin $\nu \text{C}=\text{O}$ would have appeared around 1725cm^{-1} . This is in keeping with the observation that α -substituted β -ketoesters give only chromones in Pechmann reaction⁵. The β -ketoesters (**2a-f**) on condensation with resorcinol furnished 7-hydroxy-2-methyl-3-[2-(3-methyl-4-nitro-5-isoxazolyl)-1-arylethyl]-chloromones (**3a-f**). The heterocyclization was supported by the elemental analyses, PMR (absence of ethyl group and presence of D_2O washable signal at δ 10.5) and mass spectral data of the products.

Attempted formation of isoxazolones (**5**) by he-



terocyclization of **2** with hydroxylamine led only to the open chain oxime (**4**) rather than **5** as revealed by its IR spectrum (ν_{OH} and ν_{CO} at 3400 and 1720 cm^{-1} respectively), PMR (ethyl signal) and mass spectral data. All attempts to bring about cyclization of **4** using traces of H_2SO_4 in ethanol failed, in confirmity with our earlier observation that Michael adduct could not be cyclized to 5-pyrazolones with phenylhydrazine, the products being the hydrazones⁴.

All melting points reported are uncorrected. Purity of the compounds was checked by TLC. The characterization data of the compounds **3** and **4** are given in Table 1.

Michael additions

A mixture of compound (**1a**, 2.3g, 0.01 mol), the ethyl acetoacetate (3.9g 0.03 mol) and triethylamine (30ml) was refluxed for 4 hr. After the removal of triethylamine the residue was triturated with petroleum ether and finally decomposed in methanol and filtered. Colourless crystals of Michael adduct (**2a**) were obtained from methanol. Similarly were prepared Michael adducts (**2a-f**).

Condensation of Michael adduct with resorcinol

A mixture containing compound (**2**, 3.6g 0.01 mol), resorcinol (1.10g, 0.01 mol) and 70% H_2SO_4 was stirred for about 1½ hr at 15°C. After some time the reaction mixture became a clear solution. A crystalline compound obtained by pouring the solution into ice water, was filtered and washed with water. Recrystallisation was effected from methanol; PMR ($\text{DMSO}-d_6$, TMS) of **3a**: δ 2.2 (s, 3H, isoxazole- CH_3), 2.25 (s, 3H, chromone- CH_3); 3.7-4.3 (m, 3H, $-\text{CH}_2-\text{CH}-$), 6.75-7.3 (ArH), 10.5 (bs, 1H, OH); Mass of **3a**: m/z 406 (M^+).

Condensation of **2** with hydroxylamine

The Michael adduct (**2**, 3.6g 0.01 mol) and hydroxylamine (0.33g, 0.01 mol) were refluxed in ethanol. After 10 min the reaction mixture became a clear solution. The refluxing was continued for further 3 hr, cooled and poured into ice water. A crystalline compound which separated out was filtered and washed with water. Recrystallisation was effected from aq. methanol; PMR ($\text{DMSO}-d_6$, TMS) of **4a**: δ 1.0 (t, 3H- OCH_2CH_3), 2.0 (s, 3H, isoxazole- CH_3), 2.06 (s, 3H, OCCH_3), 3.10-3.5 (m, 3H, CH_2-

Table 1—Characterization Data of Chromones (**3a-f**) and Oximes (**4a-f**)

Compd	m.p. (°C)	Mol. formula (M ⁺)	Found (%) (Calc.)		
			C	H	N
Heterocyclisation of 2a-f with resorcinol					
*3a	237	C ₂₂ H ₁₈ N ₂ O ₆ (406)	65.2 (65.3)	6.8 6.9	4.4 4.5)
*3b	180	C ₂₂ H ₁₇ N ₃ O ₈	58.5 (58.6)	9.3 9.4	3.7 3.8)
*3c	220	C ₂₃ H ₂₀ N ₂ O ₆	65.7 (65.8)	6.6 6.7	4.7 4.8)
*3d	225	C ₂₂ H ₁₈ N ₂ O ₆ Cl	60.0 (60.1)	6.3 6.4	4.1 4.2)
*3e	246	C ₂₂ H ₁₈ N ₂ O ₆ Cl	60.1 (60.2)	6.4 6.5	4.2 4.3)
*3f	230	C ₂₃ H ₂₀ N ₂ O ₇	63.3 (63.4)	6.4 6.5	4.5 4.6)
Condensation of 2 with hydroxylamine					
†4a	196	C ₁₈ H ₂₁ N ₃ O ₆ (375)	57.6 (57.8)	11.2 11.3	5.6 5.7)
†4b	212	C ₁₈ H ₂₀ N ₄ O ₈	51.4 (51.5)	13.3 13.4	4.7 4.8)
†4c	190	C ₁₈ H ₂₀ N ₃ O ₆ Cl	52.8 (52.9)	10.2 10.3	4.8 4.9)
†4d	195	C ₁₉ H ₂₃ N ₃ O ₆	58.6 (58.7)	10.7 10.8	5.9 6.0)
†4e	198	C ₁₈ H ₂₀ N ₃ O ₆ Cl	52.8 (52.9)	10.2 10.3	4.8 4.9)
†4f	205	C ₁₉ H ₂₃ N ₃ O ₇	56.2 (56.3)	10.3 10.4	5.6 5.7)

*Period of refluxing 1½ hr.

†Period of refluxing 3 hr.

CH-CH), 3.8 (*q*, 2H, CH₂-), 7.1 (*s*, 5H, ArH), 9.0 (*s*, 1H, OH, D₂O washable); Mass: *m/z* 375 (M⁺).

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Reaction of N-Alkyl/Aralkylisatoic Anhydrides with Aroylhydrazines: Formation of 1,3,4-Oxadiazoles & 1,4-Dihydro-5H-1,3,4-benzotriazepin-5-one

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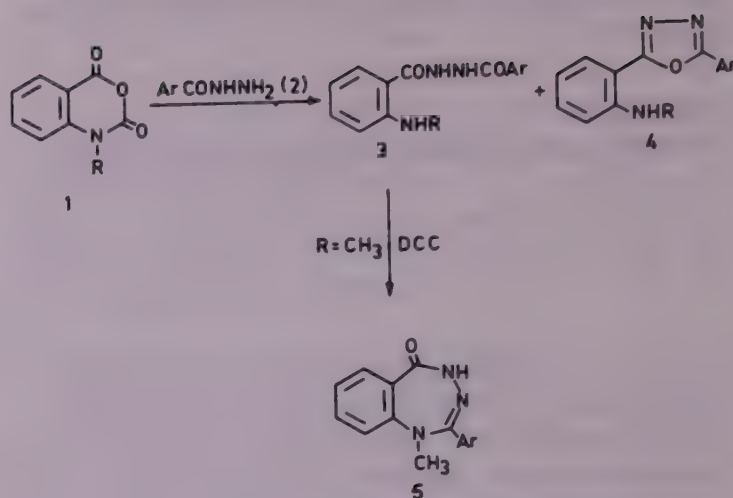
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The reaction of N-alkyl/aralkylisatoic anhydrides with aroylhydrazines in refluxing acetic acid/*p*-toluenesulfonic acid furnish 2-(2-alkylaminophenyl)-5-aryl-1,3,4-oxadiazoles (4) and 1-(2-alkylaminobenzoyl)-2-benzoylhydrazines (3). Cyclisation of 3 using DCC affords 1,4-dihydro-5H-1,3,4-benzotriazepin-5-ones (5).

Earlier, we reported the formation of 2-aryl-3,4-dihydro-5H-1,3,4-benzotriazepin-5-ones in the reaction of isatoic anhydride with aroylhydrazines¹. As an extension, presently we have studied the reaction of N-alkylisatoic anhydrides with aroylhydrazines to check the general applicability of our approach for preparing 1,4-dihydro-5H-1-alkyl-2-aryl-1,3,4-benzotriazepin-5-ones (5).

Thus N-methylisatoic anhydride (1, R = CH₃)² reacted with benzoylhydrazine (2, Ar = C₆H₅)³ in refluxing acetic acid in the presence of PTS to yield two compounds characterised as 1-(2-methylaminobenzoyl)-2-benzoylhydrazine (3, R = CH₃, Ar = C₆H₅, yield 47%) and 2-(2-methylaminobenzoyl)-5-phenyl-1,3,4-oxadiazole (4, R = CH₃,



R = CH₃, C₂H₅, CH₂C₆H₅

Ar = C₆H₅, 4-H₃CC₆H₄, 4-H₃COC₆H₄, 4-O₂NC₆H₄

Ar = C₆H₅, yield 35%). When the reaction was carried out in the absence of PTS, 3 was formed exclusively. However 3 could be converted into 4 under the original reaction conditions suggesting intermediacy 3 in the main reaction.

This reaction was extended to N-ethyl-(1, R = C₂H₅)- and N-benzyl- (R = CH₂C₆H₅)-isatoic anhydrides^{4,5} and substituted aroylhydrazines (2)⁶⁻⁸. In all the cases the corresponding 1-(2-substituted aminobenzoyl)-2-aroylhydrazines (3) and 2-(2-substituted aminophenyl)-5-aryl-1,3,4-oxadiazoles (4) were isolated (Table 1).

Attempts to prepare 1,4-dihydro-5H-1-alkyl-2-aryl-1,3,4-benzotriazepin-5-ones by the dehydra-

Table 1 — 1-(2-Alkylaminobenzoyl)-2-aroylhydrazines (3) and 2-(2-Alkylaminophenyl)-5-aryl-1,3,4-oxadiazoles (4)

Compd	Ar	m.p. (°C)	Yield (%)	Compd	Ar	m.p. (°C)	Yield (%)
3: R = CH ₃				4: R = CH ₃			
a	C ₆ H ₅	140	85	a	C ₆ H ₅	145	42
b	4-H ₃ CC ₆ H ₄	201	82	b	4-H ₃ CC ₆ H ₄	132	40
c	4-H ₃ COC ₆ H ₄	204	80	c	4-H ₃ COC ₆ H ₄	141	35
d	4-O ₂ NC ₆ H ₄	206	89	d	4-O ₂ NC ₆ H ₄	212	42
3: R = C ₂ H ₅				4: R = C ₂ H ₅			
e	C ₆ H ₅	184	80	e	C ₆ H ₅	117	39
f	4-H ₃ CC ₆ H ₄	164	81	f	4-H ₃ CC ₆ H ₄	131	40
g	4-H ₃ COC ₆ H ₄	186	84	g	4-H ₃ COC ₆ H ₄	130	42
h	4-O ₂ NC ₆ H ₄	196	82	h	4-O ₂ NC ₆ H ₄	202	37
3: R = CH ₂ Ph				4: R = CH ₂ Ph			
i	C ₆ H ₅	154	80	i	C ₆ H ₅	109	40
j	4-H ₃ CC ₆ H ₄	152	81	j	4-H ₃ CC ₆ H ₄	112	37
k	4-H ₃ COC ₆ H ₄	162	82	k	4-H ₃ COC ₆ H ₄	127	40
l	4-O ₂ NC ₆ H ₄	180	80	l	4-O ₂ NC ₆ H ₄	172	42

Satisfactory microanalyses were obtained: C ± 0.12, H ± 0.02, N ± 0.03.

tive cyclisation of **3** using polyphosphoric acid, phosphoryl chloride and anhydrous aluminium chloride, however, resulted in the exclusive formation of **4**. The desired 1,4-dihydro-5*H*-1-methyl-2-phenyl-1,3,4-benzotriazepin-5-one (**5**, Ar = C₆H₅) was formed, albeit in very low yields, when **3** (R = CH₃, Ar = C₆H₅) was refluxed with DCC in benzene. Formation of 1,4-dihydro-5*H*-1-methyl-2-aryl-1,3,4-benzotriazepin-5-ones (**5**) was also observed (vide TLC) in the DCC-assisted cyclisation reactions of 1-(2-methylaminobenzoyl)-2-arylhydrazine (**3**, R = CH₃). The isomeric compound **4** (R = CH₃) was the co-product. 1-(2-Ethylamino/benzylaminobenzoyl)-2-arylhydrazines (**3**, R = C₂H₅; CH₂C₆H₅) gave exclusively **4** under similar experimental conditions; preferred formation of **4** may be attributed to the bulkier N-alkyl group.

1-(2-Alkylaminobenzoyl)-2-arylhydrazines (**3a-l**)

A mixture of isatoic anhydride (**1**, 10 mmol) and aryl hydrazine (**2**, 10 mmol) in glacial acetic acid (5 ml) was heated under reflux for 30 min resulting in a clear solution. On cooling, **3a-l** were deposited as crystalline solids which were filtered and recrystallised from benzene (Table 1).

3a: IR(KBr): 3175, 3350 (NH), 1650, 1640 cm⁻¹ (C=O); UV(MeOH): 270 (log ε 4.13), 260 (4.17), 245 nm (4.13); PMR(DMSO-*d*₆): 62.8 (3H, NHCH₃), 1.6 (1H, NHCH₃), 7.2-8.2 (*m*, 9H aromatic), 10.2 (2H, 2 × CONH); MS: *m/z* 269 (M⁺).

2-(2-Alkylaminophenyl)-5-aryl-1,3,4-oxadiazoles (**4a-l**)

To a mixture of isatoic anhydride (**1**, 10 mmol) and *p*-toluenesulfonic acid (20 mg) in acetic acid (10 ml) was added the appropriate aryl hydrazine (**2**, 10 mmol) and the mixture heated under reflux for 9 hr. After cooling, the reaction mixture was poured slowly into cold water (250 ml), extracted with chloroform (3 × 50 ml), the chloroform layer dried (Na₂SO₄) and the solvent removed *in vacuo* to yield a gummy substance which was chromatographed over a column of neutral alumina (120-200 mesh) using petroleum ether (60-80°) and benzene as eluents. Products **4a-l** were obtained from pet. ether-benzene fractions (1:1, 5 × 20 ml) while the benzene fractions (5 × 20 ml) gave **3a-l** (Table 1).

Cyclisation of **3a-l**

Compound **3** (10 mmol) was added to freshly prepared polyphosphoric acid (10 g phosphorous pentoxide in 6 ml of phosphoric acid) and the mixture was heated for 3 hr on a steam-bath. The resulting clear solution was cooled, poured on to crushed ice (500 g) and neutralised with aq ammonia (60 ml). The precipitated **4a-l** were filtered and recrystallised from pet ether (60-80°). Cyclisation of **3** using POCl₃ or AlCl₃ also yielded **4**. Cyclisation of **3** to **4** could also be affected in refluxing acetic acid containing PTS.

1,4-Dihydro-5*H*-1-methyl-2-phenyl-1,3,4-benzotriazepin-5-one (**5**)

3 (R = CH₃, Ar = C₆H₅, 10 mmol) and DCC (3 g) in dry benzene (20 ml) was refluxed for 18 hr. The solvent was removed *in vacuo* to yield a gummy substance, which on TLC (silica gel G 100-200 mesh, chloroform-benzene 3:1) gave **5** and **4** (yield 5% & 90% respectively) (R = CH₃, Ar = C₆H₅).

4a: IR(KBr): 3300 (NH), 1610 cm⁻¹ (C=N); UV(MeOH): 253 (log ε 4.62), 280 (4.78), 375 nm (4.74); PMR(DMSO-*d*₆): δ 3.0 (*d*, 3H, NHCH₃), 1.62 (*br*, 1H, NHCH₃), 7.2-8.2 (*m*, 9H aromatic); MS: *m/z* 251 (M⁺).

5: IR(KBr): 3400 (NH), 1670 (C=O), 1610 cm⁻¹ (C=N); UV(MeOH): 245 (log ε 4.15), 250 (4.12), 280 nm (4.14); PMR(DMSO-*d*₆): δ 3.3 (*s*, 3H, CH₃), 5.9 (*br*, 1H, NH), 7.2-8.2 (*m*, 9H aromatic); MS: *m/z* 251 (M⁺).

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Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Synthesis of Imidazo[2,1-*b*]thiazoles, Imidazo[2,1-*b*][1,3]thiazin-4(3*H*)-one & Imidazo[2',1':2,3]thiazolo[4,5-*b*]quinoxaline

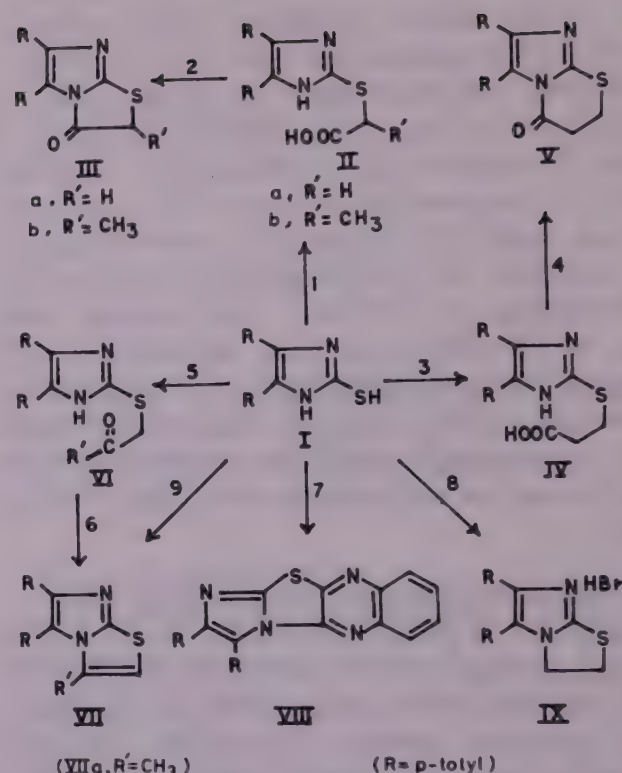
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5,6-Di-*p*-(tolyl)imidazol[2,1-*b*]thiazol-3(2*H*)-one (IIIa), its 2-methyl analogue (IIIb), 7*H*-2,3-bis-*p*-(tolyl)imidazo[2,1-*b*][1,3]thiazin-5(6*H*)-one (V) and 3-substituted-5,6-di-(*p*-tolyl)imidazo[2,1-*b*]thiazoles (VII) have been synthesised in two steps; whereas 3-methyl-5,6-di-*p*-(tolyl)imidazo[2,1-*b*]thiazole hydrochloride (VIIe), 2,3-di-(*p*-tolyl)imidazo[2',1':2,3]thiazolo[4,5-*b*]quinoxaline (VIII) and 2,3-dihydro-5,6-di-(*p*-tolyl)imidazo[2,1-*b*]thiazole hydrobromide (IX) are obtained in one step only starting from 2-mercapto-4,5-di-(*p*-tolyl)imidazole(I).

In our search for potent fungicides and bactericides, in earlier work we reported the synthesis of heterocycles containing bridgehead nitrogen atom^{1,2}. The present investigation is an extension of this work. Imidazothiazolones closely related to III have been reported in literature³.

Reaction of I with chloroacetic acid or α -bromopropionic acid in the presence of fused NaOAc gave 4,5-di-*p*-tolylimidazol-2-thioacetic acid (IIa) or α -(4,5-di-*p*-tolyl-imidazo-2-thio)propionic acid (IIb), which on treatment with acetic anhydride in the presence of pyridine underwent cyclodehydration to furnish 5,6-di-*p*-(tolyl)imidazo[2,1-*b*]thiazol-3(2*H*)-one (IIIa) or its 2-methyl analogue (IIIb) respectively. Similar fusion of I with β -bromopropionic acid furnished 7*H*-2,3-di-(*p*-tolyl)imidazo[2,1-*b*][1,3]thiazin-5(6*H*)-one (V) via the intermediate acid (IV) (Scheme 1).



(1) $R' = \text{CH}_2\text{COOH}$, NaOAc; (2 & 4) Ac_2O , pyridine; (3) $\text{BrCH}_2\text{CH}_2\text{COOH}$, NaOAc; (5) RCOCH_2Br , K_2CO_3 ; (6) PPA; (7) 2,3-dichloroquinoxaline, NaOAc; (8) $\text{BrCH}_2\text{CH}_2\text{Br}$; (9) $\text{ClCH}_2\text{COCH}_3$.

Scheme 1

Compound I on condensation with α -haloketone in absolute ethanol yielded the ketone (VI) (Table 1) which on PPA cyclization gave 3-substituted-5,6-di-(*p*-tolyl)imidazo[2,1-*b*]thiazole (VII) (Table 1). Chloroacetone on condensation with I, however, gave the cyclized product (VIIe, $R' = \text{CH}_3$) directly in good yield (Scheme 1).

Reaction of I with dibromoethane and 2,3-dichloroquinoxaline furnished in one step, the cyclised products, 2,3-dihydro-5,6-di-(*p*-tolyl)imidazo[2,1-*b*]thiazole hydrobromide (IX) and 2,3-di-(*p*-tolyl)imidazo[2',1':2,3]thiazolo[4,5-*b*]quinoxaline (VIII) respectively (Scheme 1).

Table 1—Melting Points and Analytical Data of Ketones (VI) and Imidazothiazoles (VII)

Compd	R'	m.p. °C	Mol formula	Found (Calc)%	
				N	S
VIb	<i>p</i> -Cl-C ₆ H ₄ -	125	C ₂₅ H ₂₁ N ₂ SOCl	6.9(6.5)	7.9(7.4)
VIc	<i>p</i> -NO ₂ -C ₆ H ₄ -	181	C ₂₅ H ₂₁ N ₂ SO ₃		7.8(7.2)
VI d	<i>p</i> -C ₆ H ₅ -C ₆ H ₄ -	140	C ₃₁ H ₂₆ N ₂ SO	6.3(5.9)	7.2(6.8)
VIIb	<i>p</i> -Cl-C ₆ H ₄ -	205	C ₂₅ H ₁₉ N ₂ SCl	7.2(6.8)	8.1(7.7)
VIIc	<i>p</i> -NO ₂ -C ₆ H ₄ -	125	C ₂₅ H ₁₉ N ₂ SO ₂		8.2(7.5)
VII d	<i>p</i> -C ₆ H ₅ -C ₆ H ₄ -	250(d)	C ₃₁ H ₂₄ N ₂ S	5.9(6.1)	7.5(7.0)

The structures III, V, VII, VIII and IX were established by their IR and PMR spectral data.

Compounds, IIIa, IIIb, VII ($R' = p\text{-ClC}_6\text{H}_4-$), VIII and IX were evaluated for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans* by serial plate dilution method⁴.

The minimum inhibitory concentration (MIC) of the compound IX against *S. aureus* & *C. albicans* was found to be 250 $\mu\text{g/ml}$ whereas against *Ps. aeruginosa*, it was 1000 $\mu\text{g/ml}$.

The MIC of the compound VIII may be $> 1000 \mu\text{g/ml}$ and showed activity against *C. albicans*, when tested as neat sample, and may be used for local application in form of powder or ointment provided further studies indicate absence of toxicity following local application.

2-Mercapto-4, 5-di-*p*-tolylimidazole(I)

It was prepared by heating *p*-toluoin with thiourea following the method of Bhatt *et al.*⁵. Repeated crystallization from ethanol gave I as light yellow crystals, m.p. $> 300^\circ$, yield 37.5% (Found: N, 9.7; S, 11.8. $\text{C}_{17}\text{H}_{16}\text{N}_2\text{S}$ requires N, 10.0; S, 11.4%); IR: 810 (*p*-disubstituted benzene ring), 1200 ($\nu\text{C}=\text{S}$), 1500 ($\nu\text{C}-\text{N}$), 1620 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 2625 ($\nu\text{S}-\text{H}$), 3320 ($\nu\text{N}-\text{H}$).

4,5-Di-*p*-tolylimidazole-2-thioacetic acid (IIIa; $R' = \text{H}$)

A mixture of I (2.80 g, 0.01 mol) chloroacetic acid (0.95 g, 0.01 mol), anhyd sodium acetate (0.82 g, 0.01 mol) in absolute ethanol (100 ml) was heated under reflux on a water-bath for 5 hr. The reaction mixture was concentrated, cooled to room temperature, the solid separated was filtered, washed with water and crystallised from ethanol to give IIa as colourless crystals, m.p. 218° , yield 59% (2.1 g) (Found: N, 8.1; S, 9.3. $\text{C}_{19}\text{H}_{18}\text{O}_2\text{N}_2\text{S}$ requires N, 8.3; S, 9.5%); IR: 815 (*p*-disubstituted benzene ring), 1515 ($\nu\text{C}-\text{N}$), 1600, 1610 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1690 ($\text{C}=\text{O}$ of the COOH group), 2560, 2670 (COOH), 3380 ($\nu\text{N}-\text{H}$).

IIb ($R' = \text{CH}_3$) was prepared similarly from I and α -bromopropionic acid and crystallised from ethanol in colourless crystals, m.p. 205° , yield 60% (Found: N, 7.6; S, 8.7. $\text{C}_{20}\text{H}_{20}\text{O}_2\text{N}_2\text{S}$ requires N, 8.0; S, 9.1%); IR: 820 (*p*-disubstituted benzene ring), 1500 ($\nu\text{C}-\text{N}$), 1620 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1700 ($\text{C}=\text{O}$ of the COOH group), 2625, 2700 (COOH), 3150 ($\nu\text{N}-\text{H}$).

5, 6-Di-(*p*-tolyl)imidazo[2, 1-*b*]thiazol-3(2*H*)-one (IIIa; $R' = \text{H}$)

The acid (IIa, 1 g) in a mixture of acetic anhydride (1

ml) and pyridine (3 ml) was heated on a steam-bath for 30 min. The reaction mixture was kept overnight, poured into water, and the gummy product obtained, which solidified on standing was crystallized from ethanol to allow IIIa as colourless shining flakes, m.p. 105° , yield 63.5% (0.6 g) (Found: C, 71.0; H, 4.7; N, 9.4; S, 10.4. $\text{C}_{19}\text{H}_{16}\text{N}_2\text{OS}$ requires C, 71.3; H, 5.0; N, 8.8; S, 10.0%); IR: 820 (*p*-disubstituted benzene ring), 1510 ($\nu\text{C}-\text{N}$), 1625 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1737 ($\nu\text{C}=\text{O}$); PMR (CDCl_3): δ 2.15 (6H, s, $2 \times \text{CH}_3$), 3.20 (2H, s, CH_2-CO), 7.10 (8H, ABq, ArH, C_5- and C_6 -*p*-tolyl, $J_{\text{AB}} = 9.9 \text{ Hz}$).

The acid IIb was cyclized similarly to give IIIb, which crystallized from ethanol as light yellow crystals, m.p. 96° , yield 49% (Found: C, 72.1; H, 5.6; N, 8.2; S, 9.9. $\text{C}_{20}\text{H}_{18}\text{ON}_2$ requires C, 71.9; H, 5.4; N, 8.4; S, 9.6%); IR: 810 (*p*-disubstituted benzene ring), 1490 ($\nu\text{C}-\text{N}$), 1600 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1715 ($> \text{N}-\text{C}=\text{O}$); PMR (CDCl_3): δ 2.20 (6H, d, $2 \times \text{CH}_3$), 2.30 (3H, d, C_2-CH_3), 4.20 (1H, q, C_2-H), 7.09 (4H, ABq, C_5- or C_6 -*p*-tolyl, $J_{\text{AB}} = 9.9 \text{ Hz}$), 7.15 (4H, ABq, C_5- or C_6 -*p*-tolyl, $J_{\text{AB}} = 9.9 \text{ Hz}$).

β -[4,5-Di-(*p*-tolyl)imidazole-2-thio]propionic acid (IV)

A mixture of (2.80 g, 0.01 mol), β -bromopropionic acid (1.53 g, 0.01 mol) and fused sodium acetate (0.82 g, 0.01 mol) in absolute ethanol (100 ml) was heated, under reflux for 5 hr. The reaction mixture was cooled to room temperature, poured into water, the yellow solid obtained was filtered off and crystallised from ethanol to afford IV as light yellow crystals, m.p. 234° , yield 51% (1.8 g) (Found: N, 7.7; S, 9.3. $\text{C}_{20}\text{H}_{20}\text{O}_2\text{N}_2\text{S}$ requires N, 8.0; S, 9.1%); IR: 810 (*p*-disubstituted benzene), 1510 ($\nu\text{C}-\text{N}$), 1600, 1620 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1690 ($\nu\text{C}=\text{O}$ in COOH), 2500, 2640 (OH stretching-bonded in COOH), 3150 ($\nu\text{N}-\text{H}$ stretching).

7*H*-2, 3-Di-(*p*-tolyl)imidazo[2, 1-*b*][1, 3]thiazin-5(6*H*)-one (V)

The acid (IV, 1 g) in a mixture of acetic anhydride (1 ml) and pyridine (3 ml) was heated on a steam-bath for 30 min, cooled to room temperature and poured into water. The solid, thus obtained, was crystallised from ethanol to give V as yellow shining flakes, m.p. 220° , yield 37% (0.35 g) (Found: C, 72.3; H, 5.7; N, 8.5; S, 9.9. $\text{C}_{20}\text{H}_{18}\text{ON}_2\text{S}$ requires C, 71.9; H, 5.4; N, 8.4; S, 9.6%); IR: 820 (*p*-disubstituted benzene), 1650 ($\nu\text{C}=\text{N}$), 1715 ($> \text{N}-\text{C}=\text{O}$); PMR ($\text{DMSO}-d_6$): δ 2.33 (3H, s, CH_3 , C_7 -*p*-tolyl), 2.40 (3H, s, CH_3 , C_6 -*p*-tolyl), 3.15 (2H, t, $\text{S}-\text{CH}_2$), 3.25 (2H, t, CH_2-CO), 7.08 (4H, ABq, ArH, C_7 -*p*-tolyl, $J_{\text{AB}} = 7.8 \text{ Hz}$), 7.17 (4H, ABq, ArH, C_6 -*p*-tolyl, $J_{\text{AB}} = 7.8 \text{ Hz}$).

2-*p*-Bromobenzoylmethylthio-4, 5-di-*p*-tolyl)imidazole (VIa, $R' = p\text{-Br-C}_6\text{H}_4$ -)

A mixture of I (2.80 g, 0.01 mol) and *p*-bromophenacyl bromide (2.78 g, 0.01 mol) in absolute ethanol (100 ml) was refluxed on a steam-bath for 6 hr, cooled and neutralised with aq. potassium carbonate. The solid, thus obtained, was crystallised from ethanol to VIa as orange crystals, m.p. 138°, yield 55% (2.6 g) (Found: N, 6.2; S, 6.5. $\text{C}_{25}\text{H}_{21}\text{N}_2\text{SOBr}$ requires N, 5.9; S, 6.7%); IR: 810 (*p*-disubstituted benzene), 1510 ($\nu\text{C-N}$), 1600 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 1695 ($\nu\text{C}=\text{O}$), 3350 ($\nu\text{N-H}$).

3-*p*-Bromophenyl-5,6-di-*p*-tolyl)imidazo[2,1-*b*]thiazole (VIIa, $R' = p\text{-Br-C}_6\text{H}_4$ -)

A mixture of VIa (1 g), P_2O_5 (4.0 g) and H_3PO_4 (3.0 ml) was heated in an oil-bath at 150° for 3 hr, cooled, poured into cold water with stirring and basified with aq. potassium carbonate. The resultant solid was filtered, washed with water and crystallised from ethanol to give VIIa as orange coloured crystals, m.p. 97°, yield 48% (0.4 g) (Found: C, 65.8; H, 4.4; N, 5.8; S, 7.3. $\text{C}_{25}\text{H}_{19}\text{N}_2\text{SBr}$ requires C, 65.4; H, 4.1; N, 6.1; S, 7.0%); IR: 825 (*p*-disubstituted benzene ring), 1500 ($\nu\text{C-N}$), 1620 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$).

3-Methyl-5,6-di-*p*-tolyl)imidazo[2,1-*b*]thiazole hydrochloride (VIIe, $R' = \text{CH}_3$)

A mixture of I (2.80 g, 0.01 mol) and chloroacetone (0.93 g, 0.01 mol) in abs. ethanol was refluxed on a steam-bath for 5 hr. The reaction mixture was concentrated, cooled in ice bath, the resultant solid filtered off, washed with water and crystallised from ethanol to afford VIIe as light yellow flakes, m.p. 125°, yield 54% (1.9 g) (Found: C, 67.8; H, 5.7; N, 8.3; S, 8.6. $\text{C}_{20}\text{H}_{19}\text{N}_2\text{SCl}$ requires C, 67.7; H, 5.4; N, 7.9; S, 9.0%); IR: 820 (*p*-disubstituted benzene ring), 1500, 1520 ($\nu\text{C-N}$), 1630 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 2920, 2850 ($\nu\text{C-H}$ of methyl group), 3375 ($\nu\text{N-H}$).

2,3-Di-*p*-(tolyl)imidazo[2',1':2,3]thiazolo[4,5-*b*]quinoxaline (VIII)

A mixture of I (2.80 g, 0.01 mol), 2,3-dichloroquinoxaline (1.99 g, 0.01 mol) and fused sodium acetate

(1.64 g, 0.02 mol) in absolute ethanol (60 ml) was heated, under reflux, on a steam-bath for 5 hr, concentrated and cooled. The yellow solid was filtered off, washed with water and crystallised from ethanol to furnish VIII as yellow crystals, m.p. 124°, yield 64% (2.6 g) (Found: N, 14.1; S, 8.2. $\text{C}_{25}\text{H}_{18}\text{N}_4\text{S}$ requires N, 13.8; S, 7.9%); IR: 750 (*o*-disubstituted benzene ring), 810 (*p*-disubstituted benzene ring), 1500 ($\nu\text{C-N}$), 1600 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$).

2,3-Dihydro-5,6-di-*p*-(tolyl)imidazo[2,1-*b*]thiazole hydrobromide (IX)

A mixture of I (2.80 g, 0.01 mol), 1,2-dibromoethane (1.88 g, 0.01 mol) in absolute ethanol (60 ml) was heated, under reflux, for 5 hr, cooled, poured into cold water and kept overnight. Evaporation of the solvent and crystallization from methanolic HBr gave IX which recrystallised from ethanol in colourless crystals, m.p. 252° (lit.⁶ m.p.: 258-60°), yield 60% (2.35 g) (Found: C, 58.5; H, 4.7; N, 7.7; S, 8.7. $\text{C}_{19}\text{H}_{19}\text{N}_2\text{SBr}$ requires C, 58.9; H, 4.9; N, 7.2; S, 8.3%); IR: 810 (*p*-disubstituted benzene ring), 1500 ($\nu\text{C-N}$), 1600, 1650 ($\nu\text{C}=\text{C}$ and $\nu\text{C}=\text{N}$), 3400-3300 (*br*, N-H); PMR ($\text{CDCl}_3 + \text{DMSO-}d_6$): δ 2.23 (3H, *s*, $\text{C}_6-\text{C}_6\text{H}_4-\text{CH}_3$ -*p*), 2.33 (3H, *s*, $\text{C}_5-\text{C}_6\text{H}_4-\text{CH}_3$ -*p*), 3.96 (2H, *t*, $\text{S}-\text{CH}_2$), 4.13 (2H, *t*, $>\text{N}-\text{CH}_2$), 5.10 (*bs*, 1H, NH), 7.05 (4H, *ABq*, ArH, C_6 - or C_7 -*p*-tolyl, $J_{\text{AB}} = 8.4$ Hz), 7.13 (4H, *ABq*, ArH, C_6 - or C_7 -*p*-tolyl, $J_{\text{AB}} = 8.4$ Hz).

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Reaction of 4-Aryl-2-hydrazinothiazoles with Ethyl Acetoacetate: A Reinvestigation

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The reaction of 4-aryl-2-hydrazinothiazoles (**1a,b**) with ethyl acetoacetate (**2**) affords 1-(4'-aryl-2'-thiazolyl)-3-methylpyrazol-5-ols (**3a,b**) rather than 3-arylthiazolo[2,3-c][1,2,4] triazepin-5-ones (**4a,b**) as previously reported. The correct structural assignment is based on an alternate synthesis involving reaction of phenacyl bromides (**6**) and 3-methylpyrazol-5-ol-1-thiocarboxamide (**7**). The keto/enol tautomerism of **3** has been investigated using PMR spectroscopy.

We have recently reassigned the pyrazole structure to the products obtained by the reaction of 2-hydrazinoquinolines¹ and 4-aryl-2-hydrazinothiazoles² with pentane-2,4-dione. Further, a pyrazol-5-ol structure was also established for the products obtained by the reaction of 2-hydrazinoquinolines with ethyl acetoacetate³. A seven-membered ring system was earlier proposed for all these products⁴⁻⁶. Herein we present evidence to show that the products obtained by the reaction of 4-aryl-2-hydrazinothiazoles (**1a,b**) with ethyl acetoacetate (**2**), indeed have a pyrazol-5-ol structure (**3**) instead of a thiazolotriazepin-5-one (**4**) structure proposed by several groups of workers^{4,5,7}.

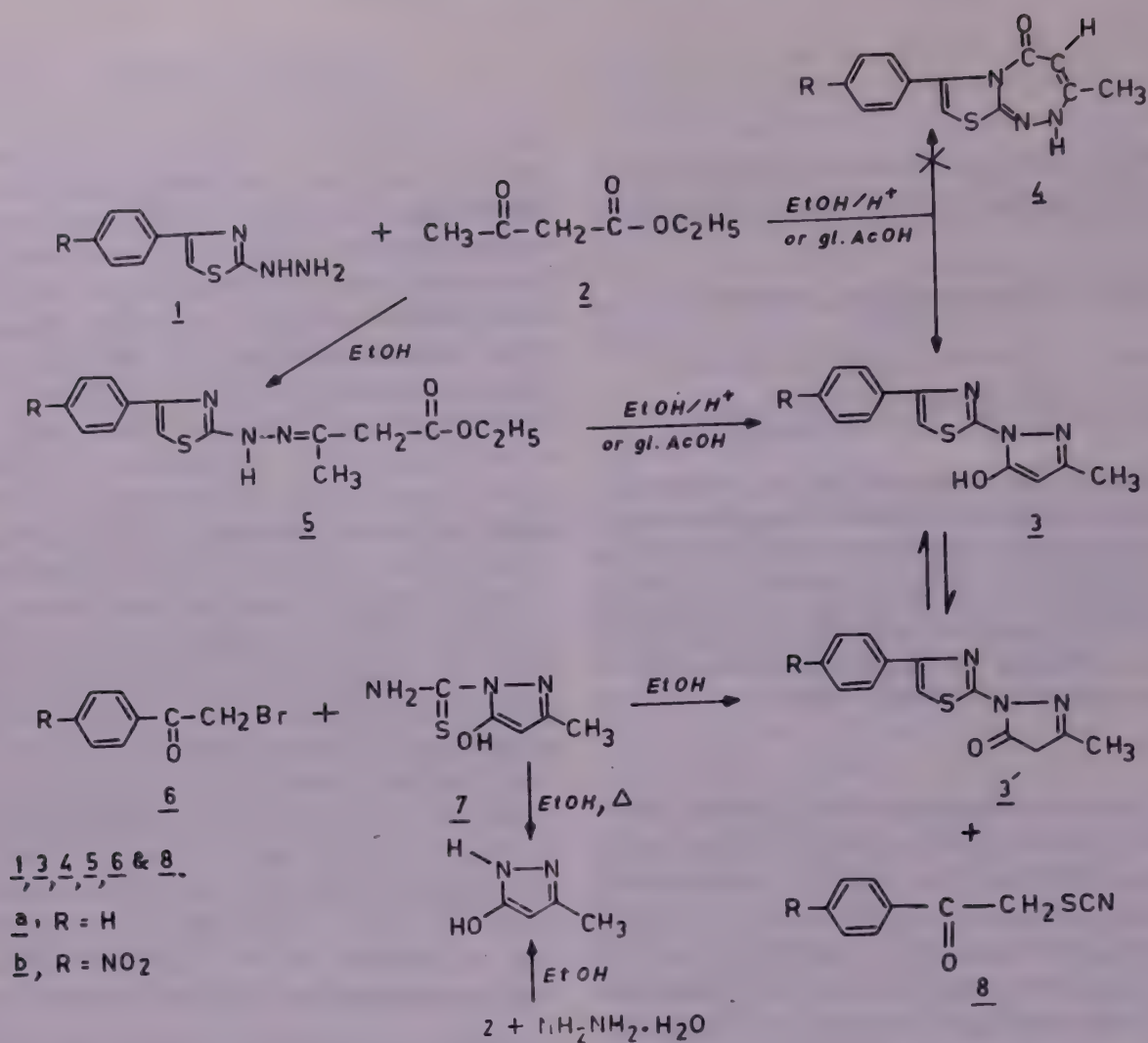
Beyer and Stehwien⁸ were the first to report the condensation of 4-phenyl-2-hydrazinothiazole (**1a**) with ethyl acetoacetate (**2**) and formulated the product as 1-(4'-phenyl-2'-thiazolyl)-3-methylpyrazol-5-ol (**3a**). Mahajan *et al.*⁴ and Dehuri *et al.*⁷ studied the same reaction and proposed a seven-membered triazepin-5-one structure (**4a**). Alaka *et al.*⁵ recently performed similar reaction by reacting 4-(*p*-nitrophenyl)-2-hydrazinothiazole (**1b**) with **2** and formulated the product as having a triazepin-5-one (**4b**) structure.

We performed the reaction of **1a,b** with **2** using similar conditions as reported by earlier workers and obtained products having m.p. 189° (lit. m.p. 192°⁴ and 196°⁸) and m.p. 218° (lit.⁵ m.p. 220-21°). Same products were obtained on carrying

out the reactions in refluxing ethanolic solution containing a few drops of HCl (m.p., m.m.p. and superimposable IR spectra). However in the absence of HCl, the corresponding hydrazones (**5a,b**) were isolated in about 60% yield. These hydrazones were characterised by PMR, IR and mass spectral data. The IR spectra of **5a** and **5b** exhibited bands at 1730 and 3300 cm⁻¹ due to ν C=O and ν NH, respectively. The PMR and mass spectral data were compatible with the assigned structure. Refluxing **5a,b** in ethanol containing a few drops of HCl or in glacial acetic acid, yielded the cyclized products in near quantitative yield. The IR spectra of these compounds show the disappearance of the original band due to ester carbonyl (1730 cm⁻¹) and in its place the appearance of a strong band at 1625 cm⁻¹. However, melting points of the hydrazones prepared by us are not in agreement with those recorded by Mahajan *et al.*⁴ and Alaka *et al.*⁵ (Table 1). But it is interesting to note that the 'intermediate' obtained by Alaka *et al.*⁵ failed to undergo cyclization in contrast to our hydrazones (**5a,b**) which underwent smooth cyclization (Scheme 1).

In order to distinguish between a 5- and 7-membered structure, an alternate synthesis was employed. Refluxing ethanolic solution of an equimolar amounts of thiosemicarbazide and **2** for 2 hr resulted in the formation of hydrazone which on dissolving in ammonia followed by the treatment with HCl yielded 3-methylpyrazol-5-ol-1-thiocarboxamide (**7**), m.p. 180° (lit.⁹ m.p. 180°). Its PMR spectrum (DMSO-d₆/CDCl₃) displayed signals at δ 2.2 (s, 3H, CH₃) and 5.1 (s, 1H, -4-H) besides broad signals centred at 3.5, 9.4 and 10.3. All these signals except at δ 2.2 were readily exchanged on shaking with D₂O. Refluxing **7** in ethanol for 4 hr yielded a product, m.p. 220° (lit.¹⁰ m.p. 215°) identical with the product obtained by treating hydrazine hydrate and **2**, thus firmly establishing a pyrazol-5-ol structure for **7**. When an ethanolic solution of **7** and an appropriate phenacyl bromide (**6**) was refluxed, products identical to those formed by the reaction of **1** and **2** were obtained in about 55% yield (m.p., m.m.p., superimposable IR and similar PMR spectral data). These products thus have structure **3** and structure **4** proposed earlier^{4,5,7} need correction. In addition to **3a**, thiocyanato ketone (**8**) was also formed in about 20% yield in agreement with our earlier observation¹¹.

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Scheme 1

Table 1 — Characterization Data of Compounds 3a, 3b, 5a and 5b

Compd	Mo. formula ($M^+ m/z$)	m.p. (lit. m.p.) °C	PMR (δ ppm)	
			CDCl_3	TFA
3a	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{OS}$ (257)	189 (192 ⁴) (196 ⁸)	2.3(s, 3H, CH_3), 3.5 (s, 2H, COCH_2), 5.4 (s, olefinic proton), 7.1-7.8 (m, 5Ar-H and a thiazole proton)	2.45(s, 3H, CH_3), 3.95 (s, 2H, CH_2CO), 7.5-7.8 (m, 5Ar-H and a thiazole proton)
3b	$\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_3\text{S}$ (302)	218 (220 ⁵)	Insoluble	2.45(s, 3H, CH_3), 3.95 & 2.60 (s, COCH_2), 6.1 (s, olefinic proton), 7.8- 8.5 (m, 4Ar-H and a thiazole proton)
5a	$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ (303)	174 (242 ⁴)	1.3(t, 3H, CH_2CH_3), 2.3(s, 3H, CH_3), 3.4(s, 2H, CH_2CO), 4.2(q, 2H, CH_2CH_3), 6.8(s, 1H, thiazol H), 7.3-7.7 (m, 5H, Ar-H), 12.6 (br, 1H, exchange- able with D_2O).	
5b	$\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$ (348)	171 (235 _s)	1.3(t, 3H, CH_2CH_3), 2.0(s, 3H, CH_3), 3.4(s, 2H, CH_2CO), 4.3(q, 2H, CH_2CH_3), 7.1 (s, 1H, thiazole H), 7.9 and 8.2 (dd, 4H, Ar-H)	

The PMR spectrum of 3a was run in CDCl_3 as well as in TFA while that of 3b, being insoluble in CDCl_3 , could be recorded only in TFA. Careful integration of the signals showed the presence of

67% enol and 33% keto form in CDCl_3 , whereas signals due to the keto form only were observed in TFA. In TFA, 3b displayed signals integrating for the existence of 25% enolic form and 75% ke-

to form. These observations suggest that the existence of keto-enol tautomers in case of **3** not only depends upon the solvent but also on the structure of the compound.

Some interesting features were noted in the mass spectral fragmentation of **3a**, **3b**, **5a** and **5b**. While in the case of **3a** and **3b**, M^+ constituted the base peak, in the case of **5a** and **5b** the base peak arose after the expulsion of 46 m.u. signifying the ready loss of elements of ethanol. Because of the low volatility of these compounds, it is difficult to speculate whether the cyclization of hydrazones is taking place under thermal or mass spectral conditions. The resultant ions, corresponding to the molecular ions of **3a** and **3b** undergo fragmentation in a particular manner. There are competitive processes occurring in the molecular ion of **3a** leading to the fission of thiazole nucleus and the sequential loss of $^*C_2OH$ and CH_3CN moieties, as already established by us in the analogous compounds^{12,13}. These processes are shown for **5a** in Scheme 2. However, the presence of nitro grouping in **3b** and **5b** triggers alternative low energy pathways thus effectively suppressing these characteristic processes.

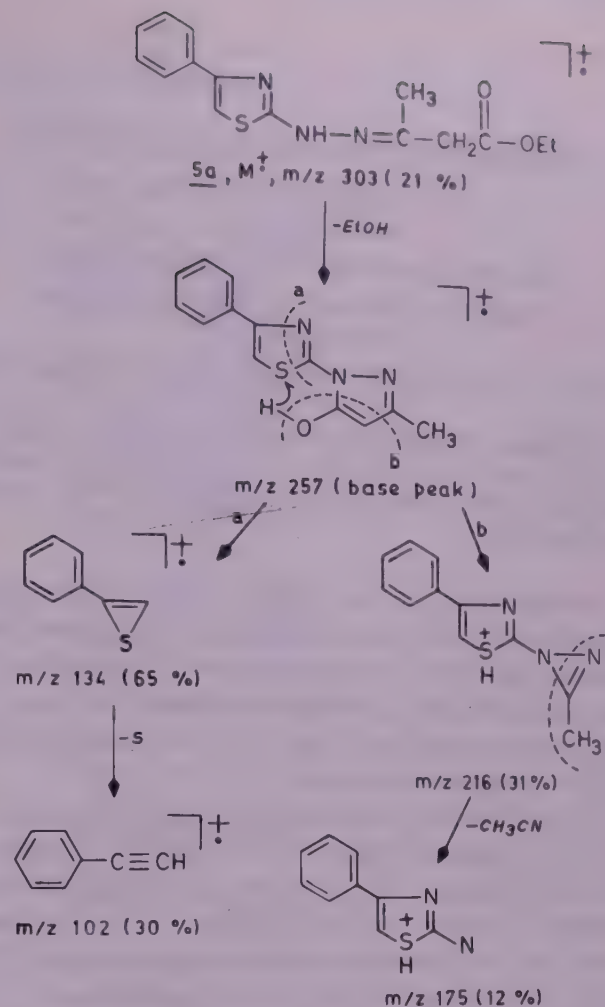
Finally, in view of our results¹⁻³ as well as the recent observations of Peet *et al.*¹⁴, synthetic design of seven-membered ring systems should require a careful consideration of the competitive five- or six-membered ring closures which are usually favoured from acyclic precursors.

We are grateful to the CSIR and UGC, New Delhi for financial assistance and to Dr Ilpokorhonen, University of Jyväskylä, Finland for mass spectral data. We also thank the Chairman, Chemistry Department for providing laboratory facilities.

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A Novel Synthesis of *s*-Triazolo[3,4-*b*]-[1,3,4]thiadiazole Derivatives

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6-Arylamino-3-aryloxymethyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (III) have been synthesised by the condensation of 4-amino-3-aryloxymethyl-5-mercapto-1,2,4-triazoles (I) with phenyl isothiocyanate.

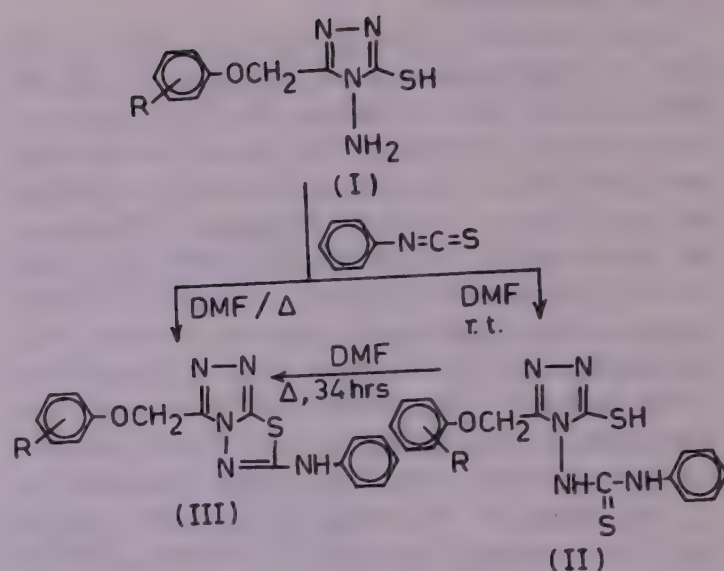
In continuation of our work on the synthesis and pharmacological activities of interesting fused ring systems such as 1,3,4-thiadiazolo[2,3-*b*]quinazolones¹ and *s*-triazolo[3,4-*b*]quinazolones², we now report a novel and new synthesis of *s*-triazolo[3,4-*b*][1,3,4]thiadiazole system.

The methods reported in literature for the preparation of *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles consist of (a) dehydrative ring closure of 4-acylamino-*s*-triazole-5-thiols³ and cyclization of 3-substituted 4-amino-5-mercapto-*s*-triazoles with cyanogen bromide^{4,5} or carboxylic acid⁶; (b) ring closure of 1,3,4-thiadiazol-2-ylhydrazines with CS₂ or cyanogen bromide⁷.

The method reported herein consists of the reaction between 4-amino-3-aryloxymethyl-5-mercapto-*s*-triazole (I) and phenyl isothiocyanate leading to the formation of 6-arylamino-3-aryloxymethyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles.

The synthon I reacted smoothly with phenyl isothiocyanate at room temperature in DMF giving the thioureas (II) in excellent yields (80-85%). Cyclodehydrosulphurization of II by heating in DMF furnished the title compounds (III) (Scheme 1). Their characterization data are given in Table 1. The same compounds were also prepared in one-step without isolating the thioureas (II). Thus, heating of I with phenyl isothiocyanate in DMF at reflux temperature for 24 hr furnished the required compounds (III). The identity of III obtained from both the paths was established by TLC, m.ps, m.m.ps, IR and PMR spectral data. The method appears to be quite general for aromatic series but fails when aliphatic isothiocyanates are used.

All the compounds thus synthesized were evaluated for their antifungal activity against *Aspergillus niger* at three different concentrations (10, 100 and 1000 ppm). The results were compared with commercial fungicide bavistin (carbendazim). Compound IIc showed activity comparable to that of



- (II) & (III) a, R = 2-CH₃
 b, R = 3-CH₃
 c, R = 4-CH₃
 d, R = 2,4-(CH₃)₂

SCHEME 1

bavistin (Table 2). Further screening of this compound on more fungi is under investigation.

1-Aryl-3-(3-aryloxymethyl-5-mercapto-*s*-triazol-4-yl)thioureas (II)

To a solution of 4-amino-3-aryloxymethyl-*s*-triazole-5-thiol (0.01 mol)⁸ in dry dimethylformamide (20 ml), an equimolar amount of phenyl isothiocyanate was added. The resulting solution was stirred for 24 hr at room temperature, and water (100 ml) added to it. The precipitated solid on recrystallization from methanol gave II (Table 1).

6-Arylamino-3-aryloxymethyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (III)

Method (A)—A solution of II (0.01 mol) in dry dimethylformamide (20 ml) was heated under reflux for 24 hr, and water (60 ml) added to it. The precipitated mass on recrystallization from ethanol gave III (Table 1).

Method (B)—To a solution of I (0.01 mol) in dry dimethylformamide (25 ml), an equimolar amount of phenyl isothiocyanate was added. The solution was heated under reflux for 24 hr and cooled when compound III separated out as a crystalline solid which was recrystallised from ethanol.

The authors express their thanks to ICAR, New Delhi for financial support and to Prof. S Giri, Head,

Table 1—Physical and Spectral Data of Compounds II and III

Compd	Yield (%)	m.p. °C	Mol. Formula	N(%)		Spectral data
				Found	Calcd.	
IIa	85	148	C ₁₇ H ₁₇ N ₅ OS ₂	18.64	18.86	IR:3252(NH), 2680(SH) PMR: δ 1.94(s, 3H, CH ₃), 3.1(s, 2H, -OCH ₂), 7.1-7.3(m, 9H, Ar-H)
IIb	80	155	C ₁₇ H ₁₇ N ₅ OS ₂	18.68	18.86	IR:3260(NH), 2682(SH) PMR: δ 2.0(s, 3H, CH ₃), 3.12(s, 2H, -OCH ₂), 7.0-7.3(m, 9H, Ar-H)
IIc	81	147	C ₁₇ H ₁₇ N ₅ OS ₂	18.50	18.86	IR:3258(NH), 2678(SH) PMR: δ 2.0(s, 3H, CH ₃), 3.2(s, 2H, -OCH ₂), 7.0-7.3(m, 9H, Ar-H)
IId	83	152	C ₁₈ H ₁₉ N ₅ OS ₂	18.23	18.19	IR:3256(NH), 2680(SH) PMR: δ 2.0(s, 6H, CH ₃), 3.12(s, 2H, -OCH ₂), 7.0-7.24(m, 8H, Ar-H)
IIIa	62	158	C ₁₇ H ₁₅ N ₅ OS	27.51	27.77	IR:3280(NH) PMR: δ 2.0(s, 3H, CH ₃), 3.14(s, 2H, -OCH ₂), 7.0-7.4(m, 9H, Ar-H)
IIIb	61	169	C ₁₇ H ₁₅ N ₅ OS	27.58	27.77	IR:3282(NH) PMR: δ 2.1(s, 3H, CH ₃), 3.2(s, 2H, -OCH ₂), 7.0-7.3(m, 9H, Ar-H)
IIIc	64	164	C ₁₇ H ₁₅ N ₅ OS	27.62	27.77	IR:3278(NH) PMR: δ 2.0(s, 6H, CH ₃), 3.1(s, 2H, -OCH ₂), 7.1-7.4(m, 9H, Ar-H)
IIId	61	157	C ₁₈ H ₁₇ N ₅ OS	19.62	19.94	IR:3274(NH) PMR: δ 2.0(s, 6H, CH ₃), 3.1(s, 2H, -OCH ₂), 7.0-7.3(m, 8H, Ar-H)

Table 2—Fungicidal Data of Compounds II and III against *A. niger*

Compd	Inhibition (%) after 96 hr at		
	1000 ppm	10 ppm	10 ppm
IIa	60	45	23
IIb	56	41	21
IIc	89	79	70
IId	53	40	19
IIIa	55	36	16
IIIb	60	43	22
IIIc	63	45	25
IIId	49	31	17
Bavistin	94	82	75

Chemistry Department for providing departmental facilities.

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Synthesis of a Novel 1,4-Thiazine System

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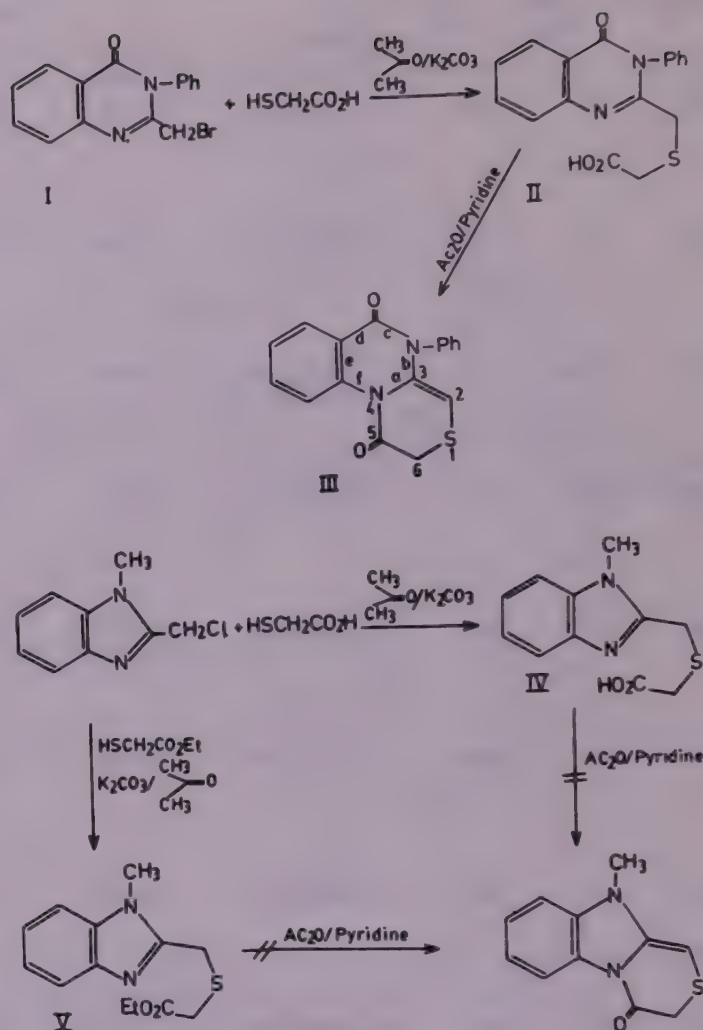
2-Bromomethyl-3-phenylquinazolin-4-one (I) reacts with thioglycolic acid to give S-[3-phenyl-4(3*H*)-oxoquinazolin-2-ylmethyl] mercaptoacetic acid (II) which on cyclization with acetic anhydride/pyridine affords 1,2,5,6-tetrahydro-5-phenyl[1,4]thiazino[4,3-*a*]quinazoline-1,6-dione (III). However, this procedure remains unsuccessful for the construction of 1,4-thiazine ring on benzimidazole ring system.

Certain fused 1,4-thiazine derivatives with a bridge head nitrogen atom have been reported for their sedative, hypnotic¹ as well as anthelmintic² activities. Thiomorpholinediones are also pharmacologically active compound. The diones on condensation with a benzene ring form an important class of 1,4-thiazine-fused heterocyclic dyes mostly used for polyester fibres³⁻⁵. S-(2-Quinolylmethyl)- and S-(2-quinazolylmethyl)-mercaptoacetic acids have been reported to give novel fused thiazines⁶ on cyclization with pyridine/acetic anhydride. Herein we report the synthesis of a cyclic enamine amide, a new 1,4-thiazine system, from 2-bromomethyl-3-phenyl-4(3*H*)-oxoquinazoline (I).

Compound I on reaction with thioglycolic acid in acetone and K₂CO₃ afforded a crystalline product (m.p. 232°), characterized as S-[3-phenyl-4(3*H*)-oxoquinazolin-2-ylmethyl]mercaptoacetic acid (II) based on elemental analysis and spectral data [C₁₇H₁₄N₂O₃S; IR(CHCl₃): 1660 and 1740 cm⁻¹ (amide and acid CO); PMR(CDCl₃, δ): 3.56 (*s*, 2H, CH₂), 3.82 (*s*, 2H, CH₂), 4.84 (*hump*, 1H, D₂O exchangeable, carboxylic OH), 7.58-8.39 (*m*, 9H, Ar-*H*); mass: *m/z* 326 (M⁺)].

Cyclization of II with acetic anhydride and pyridine gave a novel enamine type heterocyclic system characterized as 1,2,5,6-tetrahydro-5-phenyl[1,4]thiazino[4,3-*a*]quinazoline-1,6-dione (III) on the basis of elemental analysis and spectral data [C₁₇H₁₂N₂O₂S; IR(CHCl₃): 1660 and 1690 cm⁻¹ (CO); PMR(CDCl₃, δ): 7.21-8.30 (*m*, 9H, Ar-*H*), 4.9 (*s*, 1H, CH), 3.4 (*s*, 2H, CH₂); mass: *m/z* 308 (M⁺; base peak)].

Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one and tetrahydro-thiazinobenzimidazolones⁷ are biologically active compounds. This prompted us to carry out further reactions. With a view to preparing analogous thiazino-



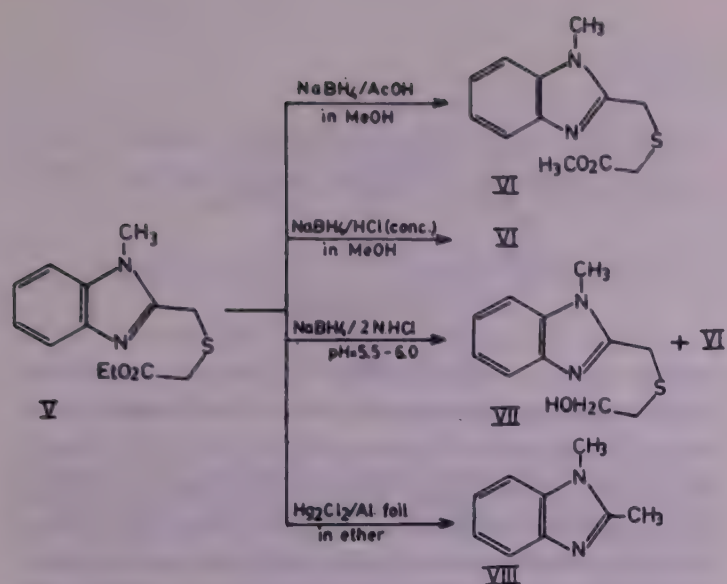
benzimidazoles, similar reaction was carried out with S-(1-methylbenzimidazol-2-ylmethyl) mercaptoacetic acid (IV). It was surprising to note that such cyclizations did not proceed with IV even in the presence of AcOH/Ac₂O, PPA, P₂O₅/benzene and also thermally. The ester of IV, ethyl S-(1-methylbenzimidazol-2-ylmethyl) mercaptoacetate (V) was also tried but cyclization again remained unsuccessful. However, the attempts for reductive cyclization of V resulted in interesting compounds.

The ester (V) in the presence of NaBH₄/AcOH in methanol or NaBH₄/HCl in methanol underwent trans-esterification to afford VI as confirmed by spectral and analytical data. However, when pH was controlled in this reaction the alcohol VII was obtained in 30% along with VI in 40% yield. 1,2-Dimethylbenzimidazole (VIII) was obtained in 40% yield when V was treated with Hg₂Cl₂ and Al foil in ether.

Reaction of 2-bromomethyl-3-phenyl-4(3*H*)-oxoquinazoline(I) with thioglycolic acid: Formation of II

To a solution of I (1 g, 0.0032 mol) in acetone (25 ml)

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were added K_2CO_3 (0.663 g, 0.0048 mol) and thioglycollic acid (0.588 g, 0.0064 mol) and the mixture was refluxed on a water-bath. The progress of the reaction was monitored by TLC. After 6 hr, the reaction mixture was filtered, acetone distilled off and the residue chromatographed over silica gel column using benzene-ethyl acetate (1:1) as eluant to give **II** in 40% yield (Found: C, 62.6; H, 4.3. $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ requires C, 62.6; H, 4.3%).

Reaction of **II** with acetic anhydride and pyridine : Formation of **III**

A mixture of **II** (500 mg), acetic anhydride (15 ml) and pyridine (10 ml) was heated on a water-bath temperature for 1 hr, and the reaction mixture poured into water and aq. layer extracted with chloroform. The combined chloroform extracts were evaporated at a low temperature and reduced pressure, and the residue was chromatographed over silica gel column using ethylacetate as eluant to give pure **III**, yield 40% (Found: C, 66.2; H, 3.9. $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ requires C, 66.2; H, 3.9%).

One of the authors (J S R) is thankful to CSIR, New Delhi for the award of a research fellowship.

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A Convenient Synthesis of 2-Methyl/ethyl- Δ^1 -pyrrolines

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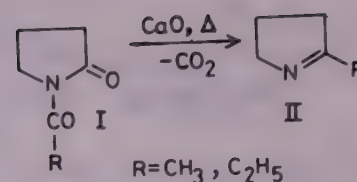
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2-Methyl/ethyl- Δ^1 -pyrrolines have been conveniently synthesised from commercially available 2-pyrrolidone.

2-Methylpyrroline was synthesised by Hielacher¹ by reacting acetylpropyl alcohol with hydrobromic acid and ammonia. Terent'ev, *et al*² synthesised it by reacting acetylpropyl alcohol with ammonia at 450° in the presence of Al_2O_3 -Pd catalyst, which resulted in a mixture containing 2-methylpyrrolidone (10%), 2-methylpyrroline (5%) and 2-methylpyrrole (20%); in the presence of Al_2O_3 alone and at 330-50° the yield of 2-methylpyrroline could be improved to 35% in the mixture. Cloke³ and Craig *et al*.⁴ synthesised 2-substituted pyrrolines by reacting γ -chlorobutyronitrile with appropriate Grignard reagents. However, these authors did not report the synthesis of 2-methylpyrroline. Gabriel⁵ developed a method for the preparation of 2-methylpyrroline by the reaction of N-chloroethylphthalimide with sodioacetoacetic ester followed by hydrolysis and decarboxylation of the resulting ester.

All the methods described above involve inaccessible starting materials and operationally cumbersome procedures. Survey of literature has revealed that myosmine⁶—a pyrroline alkaloid was synthesised by reacting nicotinoyl chloride with pyrrolidone followed by rearrangement of the resulting N-nicotinoyl derivative to myosmine. The same methodology⁶ was also adopted for the synthesis of 2-phenylpyrroline. The simplicity of this method prompted us to extend it to the synthesis of 2-methyl- and 2-ethyl-pyrrolines with slight modifications, using commercially available low cost 2-pyrrolidone.

Thus a mixture containing 2-pyrrolidone and excess acetic anhydride was refluxed for 3 hr. The re-



sulting mixture was distilled to remove unreacted acetic anhydride and acetic acid. The N-acetyl derivative (I) formed in the reaction was directly treated with excess anhydrous calcium oxide and subjected to free-flame distillation. The fraction collected at 80°-110° was the crude 2-methylpyrroline (II) which was further purified by distillation over KOH pellets, yield 42%; b.p.: 80°-85°/587 mm; PMR (CCl_4): δ 1.72 (*t*, 2H, C_3 -methylene, $J=9$ Hz), 1.92 (*s*, 3H, C_2 -methyl), 2.43 (*t*, 2H, C_4 -methylene, $J=9$ Hz), and 3.55-3.85 (*m*, 2H, C_5 -methylene).

2-Ethylpyrroline was also synthesised using propionic anhydride in place of acetic anhydride, in the above reaction; yield 52%; b.p.: 114°-18°/587 mm; PMR (CCl_4): δ 1.05 (*q*, 2H, C_2 - CH_2 - CH_3 , $J=9$ Hz), 1.80 (*t*, 3H, C_2 - CH_2 - CH_3 , $J=9$ Hz), 1.95-2.57 (*m*, 4H, C_3 - and C_4 -methylenes) and 3.52-3.85 (*m*, 2H, C_5 -methylene).

The identity of the compounds was further confirmed by the elemental analyses and IR spectrum for the absence of carbonyl group.

Further work is in progress to study the mechanistic aspects of this rearrangement and the feasibility of extending this reaction to other N-acyl, N-aroyl and N-heteroaroyl pyrrolidones.

The authors wish to thank Shri P R S Rao, Chairman-cum-Managing Director of Hindustan Photo Films for encouragement.

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A Versatile Synthesis of 2-Aryl-3,4-dihydro-4-oxobenzofuro[3,2-*d*]pyrimidines

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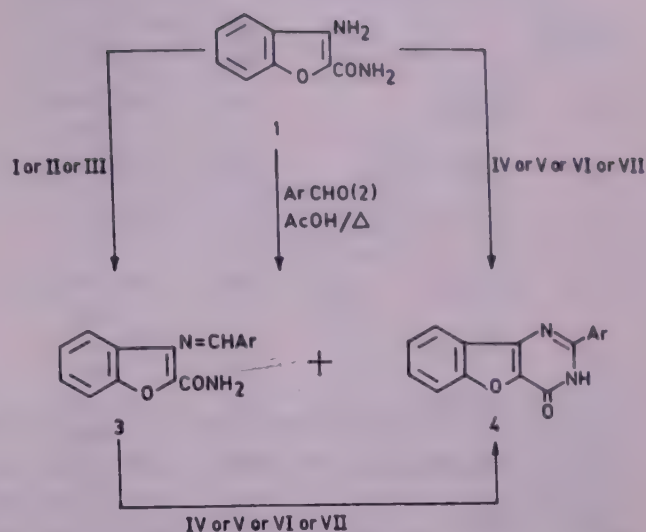
Reaction of 3-aminobenzofuran-2-carboxamide (**1**) with aromatic aldehydes (**2**) in acetic acid results in 3-*N*-(arylideneamino)benzofuran-2-carboxamides (**3**) and 2-aryl-3,4-dihydro-4-oxobenzofuro[3,2-*d*]pyrimidines (**4**) at steam-bath temperature. The reaction at room temperature yields only **3**. Dehydrogenative cyclisation of **3** gives **4**.

The reaction of 3-aminobenzofuran-2-carboxamide (**1**) with acid chlorides under basic conditions has been reported to yield pyrimidobenzofurans¹. However, the reaction of **1** with aromatic aldehydes does not seem to have been investigated. The results of reactions of **1** with various aromatic aldehydes are presented in this note.

Reaction of **1** with 4-methoxybenzaldehyde (**2**) in equimolar proportions in acetic acid or in MeOH/piperidine at ambient temperature resulted in the formation of 3-*N*-(*p*-methoxybenzylideneamino)-benzofuran-2-carboxamide (**3**), as revealed by its IR, PMR and mass spectral data. However, the above reaction when carried out at steam-bath temperature afforded two crystalline products, one of which was identical (m.m.p., Co-IR) with **3**, obtained above. The other compound which melted at 306° was characterised on the basis of IR, PMR and mass spectral data as 2-(4-methoxyphenyl)-3,4-dihydro-4-oxobenzofuro[3,2-*d*]pyrimidine (**4**) (Scheme 1). The structure **4** was further confirmed by direct comparison with an authentic sample prepared unambiguously as follows:

The reaction of 3-aminobenzofuran-2-carboxamide with 4-methoxybenzoyl chloride under Schotten-Bauman reaction conditions resulted in 3-(4-methoxybenzoyl)amino-2-benzofuran carboxamide, which on cyclisation afforded **4** in basic medium.

The reaction of **1** at ambient temperature or at steam bath temperature was extended to six other aromatic aldehydes, viz. benzaldehyde, 4-methyl-, 4-chloro-, 4-hydroxy-, 4-nitro-, and 3-nitrobenzaldehydes to see the generality of the reaction. The reaction in acetic acid at room and steam-bath tem-



SCHEME 1

peratures, in each case yielded **3** and a mixture of **3** and **4** respectively (Table 1).

The reaction of **1** with aromatic aldehydes in refluxing methanol in the presence of catalytic amount of hydrochloric acid or *p*-toluenesulphonic acid exclusively yielded **4**.

The dehydrogenative cyclisation of **3** to **4** by refluxing **3** in acetic acid or in methanol/*p*-toluenesulphonic acid, shows the intermediacy of **3** in the formation of **4**.

The reaction of 3-aminobenzofuran-2-carboxamide (**1**) with benzylideneaniline in acetic acid in equimolar proportions at room temperature yielded 3-*N*-(benzylideneamino)-benzofuran-2-carboxamide (**3**). However, the same reaction in 1 : 2 molar proportions at steam-bath temperature furnished **4** and benzylaniline. Here, the benzylideneaniline not only acts as a source of aldehyde but also as hydrogen acceptor. These reactions have been extended to six other arylideneanilines and in each case the respective **3** and **4** were obtained in quantitative yields.

Condensation of 3-aminobenzofuran-2-carboxamide (1**) with aromatic aldehydes:**

(i) *At ambient temperature*

An equimolar mixture of **1** (10 mmol) and aromatic aldehyde (**2**, 10 mmol) was dissolved in glacial acetic acid (10 ml) and kept aside at room tempera-

Table 1—Physical Data of 3-N-(Arylideneamino)-2-benzofurancarboxamides (**3**) and 2-Aryl-3,4-dihydro-4-oxobenzofuro[3,2-*d*]pyrimidines (**4**)

Compd	Ar	m.p. (°C)	Mol. formula (M ⁺)
3a	C ₆ H ₅	217	C ₁₆ H ₁₂ N ₂ O ₂ (264)
3b	4-H ₃ COC ₆ H ₄	200	C ₁₇ H ₁₄ N ₂ O ₃ (294)
3c	4-H ₃ CC ₆ H ₄	215	C ₁₇ H ₁₄ N ₂ O ₂ (278)
3d	4-ClC ₆ H ₄	202	C ₁₆ H ₁₁ N ₂ O ₂ Cl (298)
3e	4-O ₂ NC ₆ H ₄	245	C ₁₆ H ₁₁ N ₃ O ₄ (309)
3f	4-HOC ₆ H ₄	230	C ₁₆ H ₁₂ N ₂ O ₃ (280)
3g	3-O ₂ NC ₆ H ₄	243	C ₁₆ H ₁₁ N ₃ O ₄ (309)
4a	C ₆ H ₅	303	C ₁₆ H ₁₀ N ₂ O ₂ (262)
4b	4-H ₃ COC ₆ H ₄	306	C ₁₇ H ₁₂ N ₂ O ₃ (292)
4c	4-H ₃ CC ₆ H ₄	308	C ₁₇ H ₁₂ N ₂ O ₂ (276)
4d	4-ClC ₆ H ₄	310	C ₁₆ H ₉ N ₂ O ₂ Cl (296)
4e	4-O ₂ NC ₆ H ₄	255	C ₁₆ H ₉ N ₃ O ₄ (307)
4f	4-HOC ₆ H ₄	310	C ₁₆ H ₁₀ N ₂ O ₃ (278)
4g	3-O ₂ NC ₆ H ₄	250	C ₁₆ H ₉ N ₃ O ₄ (307)

Satisfactory analytical data obtained: C ± 0.042; H ± 0.02; N ± 0.32.

3b: IR (KBr): 3350-3100 cm⁻¹ (—NH₂), 1690 cm⁻¹ (C=O) PMR (DMSO-*d*₆): δ 3.78 (*s*, 3H, —OCH₃), δ 7.05-8.06 [*m*, 10H, (8H aromatic & 2H —CONH₂)], δ 9.168 (*s*, 1H, CH=N); M⁺ at *m/z* 294.

4b: IR (KBr): 3900-3000 cm⁻¹ (NH), 1690 cm⁻¹ (C=O) PMR (DMSO-*d*₆): δ 3.87 (*s*, 3H, —OCH₃), δ 7.8 [*m*, 9H (8H, aromatic & 1H, NH)]; M⁺ at *m/z* 292.

ture for 4 hr. Crystalline **3** that separated from the reaction mixture was filtered, dried and recrystallised from ethanol, yield: 48-95%.

(ii) At steam bath temperature

Compound (**1**, 10 mmol) was dissolved in glacial

acetic acid (10 ml) and appropriate aldehyde (**2**, 10 mmol) added to it. The reaction mixture was heated on a steam-bath for 3 hr, cooled, and diluted with water. The gummy material obtained was passed through a column of neutral alumina using benzene and ethyl acetate (9 : 1 & 1 : 1) as eluents to afford **3** and **4** respectively. Compounds **3** and **4** were recrystallised from ethanol and aq. dimethyl sulphoxide respectively, yield: **3**, 20-30%; **4**, 25-50%.

(iii) In refluxing methanol in presence of HCl

To a methanolic solution (30 ml) of **1** (10 mmol), aromatic aldehyde (**2**, 10 mmol) and hydrochloric acid (0.05 ml) were added. The reaction mixture was refluxed on a steam-bath for 1 hr, the separated colourless crystalline **4** filtered, washed with a little water (10 ml), dried and recrystallised from dimethyl sulphoxide, yield: 70-85%.

(iv) To a mixture of **1** and **2**, *p*-TSA was added in catalytic amount and the reaction was worked out as in (iii) above to afford **4**.

Condensation of 3-aminobenzofuran-2-carboxamide (**1**) with schiff bases: General procedure

(a) A solution of **1** (10 mmol) in acetic acid was added dropwise to a solution of the schiff base (**2**, 10 mmol) in acetic acid (5 ml) with stirring. The reaction mixture was kept aside for 4 hr. The separated product **3** was filtered, washed with pet ether (60-80°, 20 ml), dried and recrystallised as above, yield: 45-50%.

(b) The above reaction when carried out in 1 : 2 molar ratio gave exclusively **4**, which was washed with a little acetic acid (10 ml), dried and recrystallised as above. The acetic acid filtrate yielded the corresponding substituted arylanilines, yield 60-80%.

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A Convenient Synthesis of Carbamazepine (Tegretol)

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A two-step efficient procedure for the preparation of carbamazepine (3), involves intermediate preparation of N-cyanodibenz[*b*, *f*]azepine (2). Hydrolysis of 2 affords 3 in 73% yield.

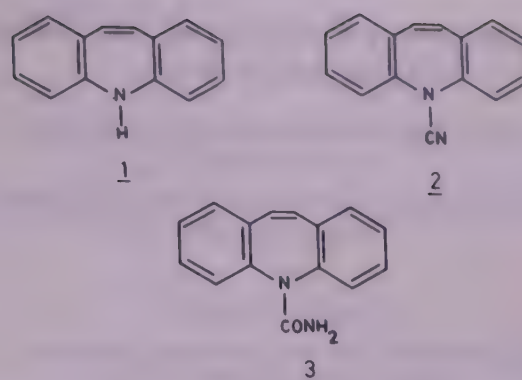
Carbamazepine (3), a drug containing 5H-dibenz[*b*, *f*]azepine ring system, is particularly effective in psychomotor epilepsy, jacksonian epilepsy and grand mal.¹⁻³ On the other hand, several derivatives of 10, 11-dihydro-5H-dibenz[*b*, *f*]azepine have been found to exhibit high anti-tumour activity.⁴ So far the main ring system has been synthesised by various methods,^{5,6} but the synthesis of substituted 3 was first achieved by Schlindler,⁷ followed by Sinha *et al.*⁸ Herein we report a convenient, two-step synthesis of 3 in overall 73% yield, starting from 5H-dibenz[*b*, *f*]azepine (1). Our approach is essentially an extension of the method of Sinha *et al.*,⁸ with some modifications. However, bulk yield and simplicity renders our approach advantageous.

In our approach starting 1 is treated with BrCN to obtain 5-cyano derivative (2) which on hydrolysis with 10% HCl gives the desired 3 in 73% yield.

Melting point was recorded in a glass capillary tube and is uncorrected. Purity of the compounds was checked by TLC (silica gel 254 S.I.F. precoated aluminium cards).

Reaction of 5H-dibenz[*b*, *f*]azepine (1) with BrCN: Formation of 5-cyanodibenz[*b*, *f*]azepine (2)

To a solution of 1 (1 g) in chloroform (20 ml) was added freshly prepared cyanogen bromide (0.7 g, 1.2 mol) under cooling and constant stirring. Stirring was continued for about 30 min more, when 1. HBr separated out as a white crystalline solid which was filtered. The filtrate was washed with water, dried and freed of the solvent under reduced pressure. The



resulting light brown semi-solid (0.53 g) showed a single spot on TLC and was characterized as 2; IR (CHCl₃): 2220 (C≡N) cm⁻¹; MS: *m/z* 218.0838 (M⁺) (Calc. for C₁₅H₁₀N₂: 218.0844, 40) and 192.0821 (Calc. for C₁₄H₁₀N: 192.0813, 100).

Hydrolysis of 3 with 10% HCl: Formation of carbamazepine (3)

Compound 2 (0.25 g) was taken in 10% hydrochloric acid (5 ml) and stirred on a boiling water-bath for 1 hr. It was cooled at room temperature, basified with ammonia and extracted with ethyl acetate. The organic extract was dried (Na₂SO₄) and concentrated to afford 3 as a crystalline solid, which recrystallized from methanol as flowers of needles (yield 73%), m.p. 203-5°; IR (CHCl₃): 3440, 3120, 1660 and 1590 cm⁻¹ (Found: C, 76.3; H, 5.1; N, 11.8. Calc. for C₁₅H₁₂N₂O: C, 76.0; H, 5.3; N, 11.7%); MS: *m/z* 236.0957 (M⁺) (Calc. 236.0949) (rel. int 28%), 192.0824 (Calc. for C₁₄H₁₀N: 192.0813) (rel. int 100%), 165, 149, 96 and 75.

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Stereoselective Synthesis of 5 α ,7 β -Dicyanocholestan-6-ones

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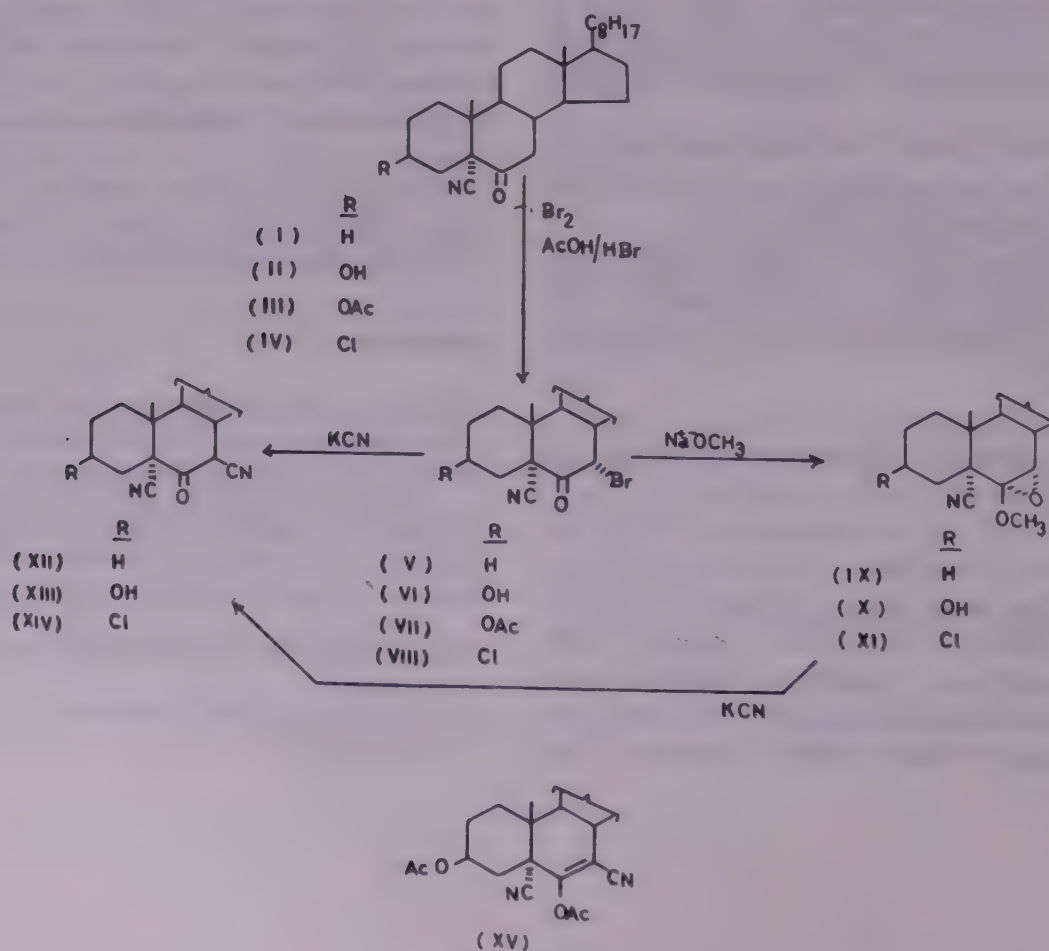
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7 α -Bromo-5 α -cyanocholestan-6-ones (V-VIII), obtained by bromination of the corresponding 6-ones (I-IV), on treatment with potassium cyanide solution afford the stereoselective 5 α ,7 β -dicyanocholestan-6-ones (XII-XIV). In order to introduce a methoxy group at C-7, the bromoketones (V-VIII) have been treated with sodium methoxide. However, this reaction, instead of giving the expected 7-methyl ethers, furnishes 5 α -cyano-6 β -methoxy-6 α ,7 α -oxidocholestanes (IX-XI) which on KCN treatment give back the 5 α ,7 β -dinitriles (XII-XIV).

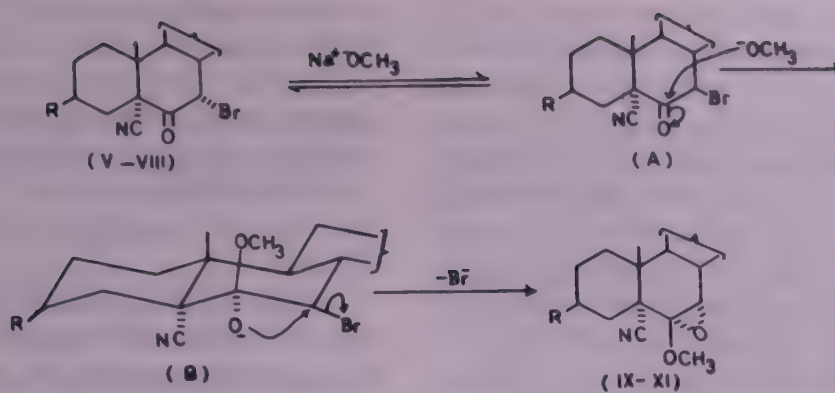
Synthesis of 5 α -cyanocholestan-6-ones (I-IV) has been reported earlier¹. We have now treated these cy-

anoketones with bromine solution in acetic acid containing few drops of HBr at 0-5° with a view to synthesizing the dicyanoketones (while brominating II, acetic acid was not used). The sole products were characterized as 7 α -bromo-5 α -cyanocholestan-6-ones (V-VIII). The IR spectra of these compounds showed absorption bands due to C $\equiv$ N (2230-2240), C=O (1720-1730) and C-Br (620-660 cm⁻¹) functions. Their PMR spectra exhibited a one-proton doublet at δ 4.40 (J = 3 Hz) ascribable to the C₇-proton. The coupling constant suggested the orientation of this proton as equatorial, and hence the incoming bromine as axial (α -oriented).

7 α -Bromoketones (V-VIII) on reaction with potassium cyanide gave 7 β -nitriles (XII-XIV; Scheme 1) (acetate in VII suffered hydrolysis to yield XIII, which on acetylation with Ac₂O/Py gave XV). The IR spectra of these compounds exhibited absorption bands due to C $\equiv$ N (2230-2250) and C=O (1735 cm⁻¹) functions. The orientation of C₇-cyano group in these compounds is based on the J value of 10 Hz for C₇-proton which is axially oriented. Treatment of the bromoketones with sodium methoxide provided



Scheme 1



epoxy methyl ethers (IX-XI), the IR spectra of which exhibited strong absorptions around 1230 and 1070 cm^{-1} for C-O and the absence of a carbonyl band. Based on a doublet with $J = 2$ Hz for C_7 -proton, its

orientation was assigned as β (equatorial) and thus the epoxy ring as α . The formation of these epoxy methyl ethers from α -bromoketones is not unusual^{2,3}, and is given in Scheme 2.

Table 1—Characterization Data of the Products V-XV

Compd	Yield (%)	m.p. °C	Mol. formula (M ⁺)	(Found (%) Calc.)			PMR(CDCl ₃ + DMSO-d ₆) (δ , ppm)
				C	H	N	
V	85	110	C ₂₈ H ₄₄ NOBr (489, 491; 1:1)	68.7 (68.6)	9.0 8.9	2.7 2.9	4.40 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H)
VI	70	130	C ₂₈ H ₄₄ NO ₂ Br (505, 507; 1:1)	66.3 (66.4)	8.8 8.7	2.7 2.8	4.40 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H), 4.10 (<i>m</i> , $W_1 = 20$ Hz, 1H, C ₃ - α H), 3.34 (<i>m</i> , 1H, exchangeable with D ₂ O, C ₃ -OH)
VII	80	150	C ₃₀ H ₄₆ NO ₃ Br (547, 549; 1:1)	66.6 (65.7)	8.5 8.4	2.4 2.6	5.20 (<i>m</i> , $W_1 = 18$ Hz, 1H, C ₃ - α H), 4.40 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H), 2.03 (<i>s</i> , 3H, C ₃ -OCO-CH ₃)
VIII	80	145	C ₂₈ H ₄₃ NOCIBr (523, 525, 527)	64.2 (64.2)	8.3 8.2	2.6 2.7	4.40 (<i>d</i> , $J = 3$ Hz, merged with multiplet $W_1 = 18$ Hz, 2H, C ₇ - β H and C ₃ - α H)
IX	85	140	C ₂₉ H ₄₇ NO ₂ (441)	78.8 (78.9)	10.7 10.6	3.1 3.2	3.40 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H), 3.20 (<i>s</i> , 3H, C ₆ -OCH ₃)
X	70	146	C ₂₉ H ₄₇ NO ₃ (457)	76.3 (76.1)	10.4 10.3	3.1 3.0	4.20 (<i>m</i> , $W_1 = 21$ Hz, 1H, C ₃ - α H), 3.40 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H), 3.23 (<i>s</i> , 3H, C ₆ -OCH ₃)
XI	75	137	C ₂₉ H ₄₆ NO ₂ Cl (475, 477; 3:1)	73.1 (73.2)	9.7 9.6	2.8 2.9	4.40 (<i>m</i> , $W_1 = 22$ Hz, 1H, C ₃ - α H), 3.45 (<i>d</i> , $J = 3$ Hz, 1H, C ₇ - β H), 3.20 (<i>s</i> , 3H, C ₆ -OCH ₃)
XII	80	98	C ₂₉ H ₄₄ N ₂ O (436)	79.9 (79.8)	10.2 10.1	6.4 6.4	3.90 (<i>d</i> , $J = 10$ Hz, 1H, C ₇ - α H)
XIII	70	77	C ₂₉ H ₄₄ N ₂ O ₂ (452)	76.8 (77.0)	9.6 9.7	6.1 6.2	3.90 (<i>d</i> , $J = 10$ Hz, merged with a multiplet, $W_1 = 10$ Hz for 2H, C ₇ - α H and C ₃ - α H respectively), 2.70 (<i>br s</i> , 1H, exchangeable with D ₂ O, C ₃ -OH)
XIV	75	170	C ₂₉ H ₄₃ N ₂ OCi (470, 472; 3:1)	73.8 (74.0)	9.2 9.1	5.9 6.0	4.17 (<i>m</i> , $W_1 = 20$ Hz, 1H, C ₃ - α H), 3.90 (<i>d</i> , $J = 10$ Hz, 1H, C ₇ - α H)
XV	60	145	C ₃₃ H ₄₈ N ₂ O ₄ (536)	73.7 (73.9)	9.1 8.9	5.1 5.2	2.03 (C ₃ -OCOCH ₃), 2.40 (C ₆ -OCO-CH ₃), 5.20 (<i>m</i> , $W_1 = 17$ Hz, 1H, C ₃ - α H)

The above proposal highlights two points: (a) Unlike the nucleophilic substitution at the saturated C-7 giving 7 β -cyano derivative by cyanide ion, methoxide undergoes nucleophilic addition at C₆-CO by attacking C=O from the less hindered side. (b) The oxanion as in (B) attacks the C-7 stereospecifically to effect elimination of bromide in *E2* way (Scheme 2). The oxanion and bromine, both being *syn*-periplanar (equatorial) provide necessary condition for *syn*-elimination. The epimerization of 7 α -bromo to its β -form is a must to yield α -epoxide. The explanation for the contrasting behaviour of the two ($^-$ CN and $^-$ OCH₃) is the fact that the cyanide ion being a stronger nucleophile substitutes bromine by attacking from the back side just in one stroke. But, the less nucleophilic $^-$ OCH₃, in the first instance, permits the isomerization of α -bromo to its β -analogue through enolization and then attacks C=O from the front side to yield 7 α -epoxide. The reason for this difference in the reaction trend may be the more basic nature of methoxide ion, which facilitates enolization unlike the less basic cyanide ion. However, the reaction of 7-bromoketones with KCN did not provide cyanoepoxides^{4,5}. Reaction of the epoxy derivatives (IX–XI) with potassium cyanide under similar reaction condition provided the dicyanocholestanones (XII–XIV).

Melting points are uncorrected. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer, mass spectra on a J–JMS–300D spectrometer and PMR spectra on a Varian A60 instrument using TMS as internal standard. Characterization data of the compounds V–XV are given in Table 1.

7 α -Bromo-5 α -cyanocholestan-6-ones (V–VIII)

To a solution of appropriate 5 α -cyanocholestan-6-one (I–IV)¹ (2 g) in ether (30 ml) was added a solution of bromine (6 ml) in acetic acid (10 ml) during 15 min at 0°. The reaction mixture was kept in a refrigerator for 30–48 hr and extracted with ether. The ether ex-

tract was washed successively with water, sodium bisulphite solution, water, sodium bicarbonate solution (~ 5%) and water, dried (anhyd. Na₂SO₄) and solvent removed on a steam-bath. The oily residue on crystallization from methanol afforded the corresponding 7 α -bromocholestan-6-one (V–VIII) (Table 1).

5 α -Cyano-6 β -methoxy-6 α ,7 α -oxidocholestanes (IX–XI)

7 α -Bromo-5 α -cyanocholestan-6-one (1 g) was added to sodium methoxide (50 ml; 5%) and the mixture kept under anhydrous conditions for 20–30 min, mixed with water and extracted with ether. The extract on usual work-up gave a solid which on crystallization from methanol furnished the corresponding epoxy methyl ether (IX–XI) (Table 1).

5 α ,7 β -Dicyanocholestan-6-ones (XII–XIV)

To a solution of 7 α -Bromo-5 α -cyanocholestan-6-one (2 g) in ether-methanol (50 ml; 1:1) was added KCN (2 g) and the reaction mixture kept for 2–4 hr (the reaction being monitored by TLC), mixed with a large amount of water and extracted with ether. The ether layer was washed with sodium bicarbonate solution (~ 5%), and water, dried (anhyd. Na₂SO₄), solvent removed on a water-bath and the residue crystallized from methanol to give the dicyano ketone (XII–XIV) (Table 1) as shining crystals.

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Base-catalysed Reaction of Formaldehyde with 1,3-Diaryl-1,3-propanediones

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Instead of undergoing the Mannich reaction; 1,3-diaryl-1,3-propanediones (**1**) yield 2-aryl-1,5-diaryl-1,5-pentanediones (**4**) via base-catalysed cleavage. The cleaved product is isolated as the corresponding acid. A suitable mechanism has been discussed.

1,3-Diphenyl-1,3-propanedione (**1a**) has been reported to undergo Knoevenagel type condensation with a phthalazone carboxaldehyde¹. However, 2,4-dibenzoyl-1,5-diphenyl-1,5-pentanedione (**5**) is reported to be formed when **1a** is treated with dibenzylamine and formaldehyde under acidic condition². The same compound is also reported to be formed by the reaction of **1a** with formaldehyde under basic condition³. But Crombie and co-workers⁴ contradicted the above results and claimed a possible C-C bond cleavage at the carbonyl carbon in the reaction of **1a** with benzaldehyde in the presence of a base giving 2-benzoyl-1,3,5-triphenyl-1,5-pentanedione (**6**) as the sole product and not 2,4-dibenzoyl-1,5-diphenyl-1,5-pentanedione. Such a cleavage of C-C bond under alkaline conditions has been reported⁵ for 1,3-diketones which have a high percentage of enol character. This controversy coupled with high reactivity of the central methylene group in 1,3-diaryl-1,3-propanediones (**1**) prompted us to reinvestigate the Mannich reaction on **1**.

The compounds **1b-d** were prepared by the reported method for **1a** (Table 1)⁶. Compound **1d** was prepared for the first time whereas **1b** and **1c** are known⁷.

When **1a** (1.12 g, 0.005 mol) was treated with formaldehyde (35%, aq. solution) (1 ml, 0.01 mol) in ethanol (20 ml) in the presence of morpholine (0.5 ml, 0.006 mol) at either room temperature or under reflux for 2 hr, 2-benzoyl-1,5-diphenyl-1,5-pentanedione (**4a**) was obtained. The same product was also obtained by treating **1a** with formaldehyde in the presence of different primary, secondary or tertiary amines.

Compound **4a** can exhibit keto-enol tautomerism. However, **4a** showed a $\lambda_{\max}$ at 246 nm, but no

Table 1—Physical Data of 1,3-Diaryl-1,3-propanediones (**1**)

Compound	R	R'	m.p.* °C	Yield† (%)
1a	H	H	65-66	76
1b	H	NO ₂	140-41	78
1c	OCH ₃	H	127-28	71
1d	OCH ₃	NO ₂	168-69	76

*m.p. (reported): **1a**: 76-77
1b: 161-62
1c: 130-31

†Reported yields are of the crystallised products.

band at 350 nm. The absorption band at 350 nm is characteristic of the enol form of 1,3-diketones as observed in the case of **1a** ($\lambda_{\max}$ at 350 nm)⁶. It is also known that substitution at the methylene group in a 1,3-diketone decreases the enol content remarkably^{7,9}.

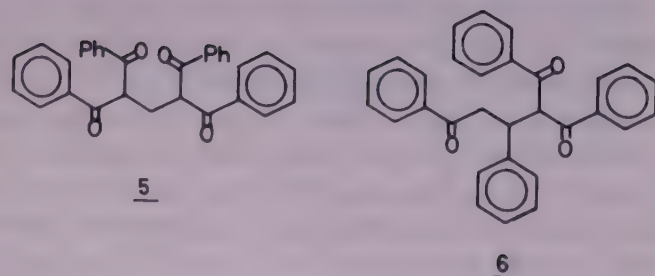
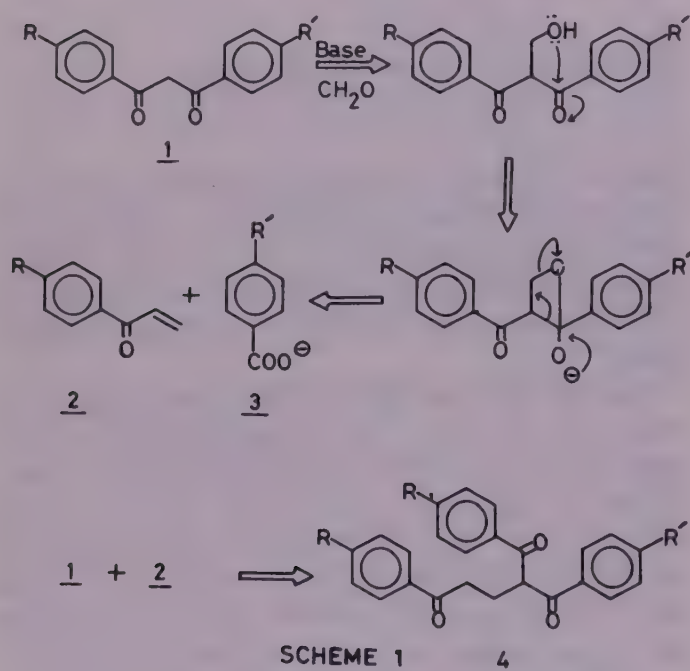
The IR spectrum (KBr) of **4a** showed peaks at 1660 and 1690 cm⁻¹ due to carbonyl groups. The PMR spectrum (CDCl₃) of **4a** exhibited two clear triplets centered at δ 2.75 (*t*, 2H, -CH₂-, *J* = 6 Hz) and 5.7 (*t*, 2H, -CO-CH₂-, *J* = 6 Hz) due to the two methylene groups and a multiplet at 7.2-8.2 (*m*, 15H) for aromatic protons. The peak position due to the protons of methylene group adjacent to the carbonyl group seemed unusual. However, from the model of the compound, it appeared that the methylene group might experience an anisotropic deshielding from the neighbouring groups. Moreover, the hydrogen at position-2 was acidic and exchangeable. In **4a**, this hydrogen would be bonded to the 5-CO group. Hence, the coupling of the adjacent carbonyl group by this proton, though the compound was in the keto-form, was not observed. In the PMR spectrum of **4c** also, the respective methylene groups appeared at δ 2.75 and 5.65 as triplets with an additional singlet at 3.9 due to the protons of the two methoxyl groups. The mass spectrum of **4a** gave the molecular ion peak at *m/z* 356. To generalise the observation, the same reaction was carried out on compounds **1b-d** which gave **4b-d** respectively (Table 2).

The plausible mechanism for the formation of **4** from **1** is depicted in Scheme 1.

According to the postulated mechanism initially a C-methylol derivative of **1** is formed. The alcoholic oxygen of the hydroxymethyl group attacks the ad-

Table 2—Physical Data of 2-Aryoyl-1,5-diaryl-1,5-pentanediones (4)

Compound	R	R'	m.p. °C	Yield (%)	Found (%) (Calc.)		
					C	H	N
4a	H	H	178-79	83	80.9 (80.9)	5.6 (5.6)	— (—)
4b	H	NO ₂	154-55	87	74.3 (74.4)	4.9 (4.9)	3.5 (3.6)
4c	OCH ₃	H	153-54	92	75.0 (75.0)	5.7 (5.8)	— (—)
4d	OCH ₃	NO ₂	167-68	91	67.6 (67.7)	4.9 (5.0)	3.0 (3.1)



jacent carbonyl carbon leading to the formation of a 4-membered transition state which decomposes to aryl vinyl ketone (2) and the substituted benzoic acid (3). The former (2) may undergo Michael addition with an additional molecule of 1 to give 4. In the case of an unsymmetrically substituted 1, the methylol oxygen would attack that carbonyl carbon which is more electron deficient. Consequently, benzoic acid corresponding to the aryl moiety undergoing the attack, would be the side product. With this in mind, when 1d was treated with formaldehyde in the presence of a base, 4-nitrobenzoic acid (3d) was obtained as the side product along with 4d. This observation supported the postulated mechanism.

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Use of Aluminium as a Friedel-Crafts Catalyst

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Toluene has been alkylated with isopropyl bromide, *n*-butyl bromide, *s*-butyl bromide *t*-butyl chloride and benzyl chloride using aluminium as a Friedel-Crafts catalyst to obtain *p*-isopropyl-, *p*-*s*-butyl-, *p*-*s*-butyl *p*-*t*-butyl- and *p*-benzyl-toluenes respectively in good yields, except in the case of *p*-(*s*-butyl) toluene which is obtained in 30% yield.

A few reports are available on the use of metal complexes¹⁻⁶, phase-transfer condition⁷ and metal oxides^{8,9} in Friedel-Crafts (F-C) reaction. Reports are also available on the use of metals as catalyst like uranium¹⁰, titanium¹¹ and aluminium amalgam¹². Herein we report the efficacy of using aluminium foil as a catalyst in F-C reaction. The advantage accruing are easy work-up and milder reaction condition (to avoid over-substitution).

Toluene (100 ml) was alkylated with isopropyl bromide (12.5 ml) by heating the two reactants together at 60-70° in the presence of aluminium foil (300 mg) for 4 hr to obtain *p*-(isopropyl)toluene or *p*-cymene (b.p. 175-80°; lit¹³ 177°). The identity of *p*-cymene was confirmed by direct comparison (co-IR) with an authentic sample.

Alkylation of toluene (100 ml) with *n*-butyl bromide (16 mg) at 70-80° for 6 hr in the presence of Al (500 mg) yielded *p*-(*s*-butyl)toluene in 30% yield, b.p. 195-98°. Alkylation of toluene (110 ml) with *s*-butyl bromide at 80-85° for 6 hr in presence of alu-

minium (300mg) also furnished the above compound in 30% yield. IR and PMR data of *p*-(*s*-butyl)toluene were consistent with its structure.

Alkylation of toluene (100 ml) with *t*-butyl chloride at 45-50° for 6 hr (amount of Al = 300 mg) yielded *p*-(*t*-butyl) toluene in 80% yield, b.p. 190-95° (lit.¹³ b.p. 193°). It was fully characterised by its IR and PMR data.

Alkylation of toluene (40 ml) with benzyl chloride (12 ml) at 95-100° (amount of Al = 100 mg) yielded *p*-benzyltoluene in 50% yield, b.p. 285-98° (lit.¹³ 286°), the IR and PMR data providing full support to the assigned structure.

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o-Phenanthroline Thiolester as a Reactive Acylating Reagent

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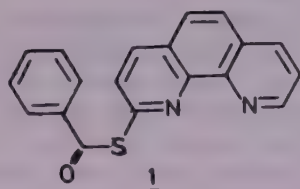
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o-Phenanthroline thiolbenzoate reacts with amines at room temperature almost instantaneously to give the amides. It reacts with alcohols in the presence of suitable metal ions such as Fe^{2+} at room temperature to afford esters in very good yields.

The total synthesis of macrolide antibiotics requires rapid esterification methods under mild conditions. Pyridine thiolesters have been successfully used for this purpose. The metal ion-assisted acyl transfer¹ is an important procedure. Metal ions such as Ag^+ or Hg^{2+} , however, have limited utility because they are expensive or toxic².

Nevertheless, no works have been reported on the successful application of *o*-phenanthroline in organic synthesis inspite of its high chelating behaviour towards all kinds of metal ions³.

We wish to report here the preparation and facile acyl transfer reaction of *o*-phenanthroline thiobenzoate (**1**)



The acylation of 2-mercapto-*o*-phenanthroline prepared by the reaction of 2-chloro-*o*-phenanthroline⁴ with sodium hydrogen sulphide, with benzoyl chloride in aqueous acetone afforded the desired **1** in 95% yield which was recrystallised from chloroform and hexane (1.1, v/v); m.p. 183-85° (Found : C, 72.2; H, 3.7; N, 8.8; S, 10.2. Regd : C, 72.1; H, 3.8; N, 8.9; S, 10.1%); IR: 1675 cm^{-1} ($>\text{C}=\text{O}$).

The reaction of **1** with one equivalent amine (R-NH_2) in chloroform solution is almost instantaneous giving the amide PhCONHR and 2-mercapto-*o*-phenanthroline: Where $\text{R} = \text{C}_6\text{H}_{11}$ (cyclohexyl), the yield of $\text{PhCONHC}_6\text{H}_{11}$ is 84%. With benzylamine, the

amide $\text{PhCONHCH}_2\text{C}_6\text{H}_5$ is obtained in 82%. In either case the 2-mercapto derivative is recovered in more than 80% yield.

Compound **1** also reacts with alcohols such as benzyl alcohol and methanol under refluxing conditions in chloroform medium to furnish $\text{PhCOOCH}_2\text{Ph}$ and PhCOOMe in 89 and 80% yields respectively. The recovery of 2-mercapto derivative in the case of methanol is 93% while in the case of benzyl alcohol it is 82%.

In any case, poor solubility or acidic property of 2-mercapto-*o*-phenanthroline, enables easy separation of the amides or esters from the reaction mixture.

Next, We investigated the metal ion-assisted acyl transfer to alcohols in the presence of ferrous ion at room temperature. Thus to a suspension of anhydrous ferrous chloride (1 eq) and *o*-phenanthroline thiolbenzoate (**1**) in chloroform (or dichloromethane)-tetrahydrofuran (THF) mixture was added methanol (5 eq) at room temperature. Immediate colour change from reddish brown to red was observed, and a brownish violet complex was precipitated in a few minutes. After stirring for 8 hr at room temperature, methyl benzoate was isolated in 85% yield by conventional work-up. The precipitated complex had no carbonyl group and was insoluble in common organic solvents. 2-Mercapto-*o*-phenanthroline was recovered easily by treatment of the complex with aq. sodium hydroxide solution followed by the neutralisation with acetic acid. The results under similar conditions involving other metal ions are summarised in Table 1. In the case of the cobalt(II) chloride immediate precipitation of the complex decreased the yield of the product esters.

Table 1 — Metal Ion-assisted Acyl Transfer Reaction

ROH	Metal ion ^a	Yield (%) ^b of PhCOOR
MeOH	FeCl_2	85
PhCH_2OH	FeCl_2	92
$\text{C}_2\text{H}_5\text{OH}$	FeCl_2	80
$\text{C}_6\text{H}_{11}\text{OH}$	FeCl_2	80
H_2O	FeCl_2	82
MeOH	FeCl_2^c	79
MeOH	FeCl_2^d	37
MeOH	FeCl_3	58
MeOH	CoCl_2	24
MeOH	NiCl_2	19

^aOne equivalent. ^bIsolated yield. ^cTwo equivalents. ^d1/2 Equivalent.

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In summary, *o*-phenanthroline thiol ester is highly reactive acylating reagent towards amines, and also effective towards alcohols in the presence of Fe^{2+} ion under mild conditions.

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Reaction of Acetophenone with Potassium Hydroxide in Diethylene Glycol

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The reaction of acetophenone with potassium hydroxide in diethylene glycol under reflux furnishes 2-methyl-4, 6-diphenylbenzophenone (A).

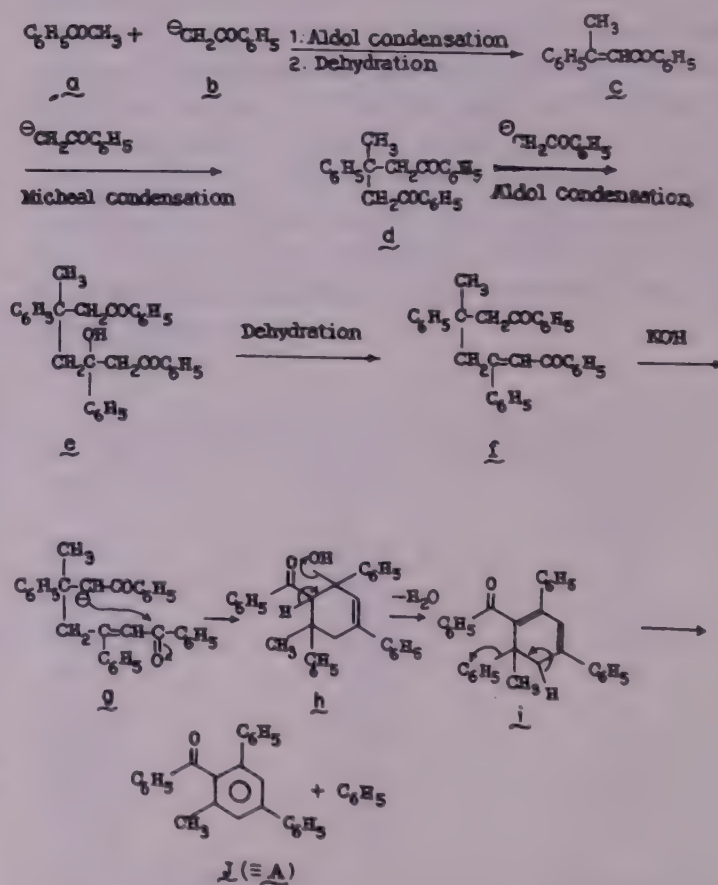
In a previous communication¹ from this laboratory ketones with or without α , β -unsaturation were shown to furnish the saturated epimeric alcohols on reaction with potassium hydroxide in diethylene glycol. A reverse process of the reaction has also been reported² where cholesterol is oxidised to cholesta-3, 5-diene and cholesta-5, 7 -dinene-3, 6-diol-benzophenide on refluxing with potassium hydroxide in an aprotic solvent like dimethyl sulphoxide. In continuation of our study on the reductive effect of potassium hydroxide we ventured our attempt on an α , β -unsaturated ketone which is in conjugation with an aromatic ring. In order to prepare such a compound we took up acetophenone as an ideal starting material which is reported^{3,4} to give 1, 3-diphenyl-2-buten-1-one under basic condition. The C-C double bond formed by Aldol condensation of acetophenone and subsequent dehydration is expected to be particularly stable as it is in conjugation with the aromatic ring. We report in this note the isolation of a product formed by condensation of acetophenone alone or with 1, 3-diphenyl-2-buten-1-one (c) on refluxing with potassium hydroxide in diethylene glycol.

The compound A obtained by refluxing a mixture of acetophenone and KOH in diethylene glycol (*vide infra*) was analysed for $C_{26}H_{20}O$. Its IR spectrum showed an absorption band at 1660 indicative of an α , β -unsaturated carbonyl group and the sharp peaks at 1280, 1270, 940, 880, 775, 760, 750, 720, 700 cm^{-1} due to aromatic nucleus. Its UV absorption at 245 nm with a high absorption coefficient (ϵ , 30,000) was typical of biphenyls⁵. Its mass spectrum exhibited the molecular ion peak at m/z 348 (M^+) with other peaks at m/z 271 ($M-C_6H_5$)⁺, 242 ($M-C_6H_5CO$)⁺, 228, 165 ($171-C_6H_5$)⁺, 105 (C_6H_5CO)⁺, and 77 (C_6H_5)⁺.

The PMR spectrum of A showed a three proton singlet at δ 2.22 assignable to an aromatic methyl group and a cluster of peaks at 7.0-7.7 due to 17 aromatic protons. A combination of SFORD and B-B decoupled experiments of ^{13}C NMR showed the

presence of a quarter centered at δ 19.7 due to the methyl carbon in an aromatic ring and doublets centered at 126.1, 127.1, 127.2, 127.6, 127.9, 127.95, (2C), 128.2 (2C), 128.2 (2C), 129.1 (2C), 129.2 (2C), and 132.9 (2C) due to 17 protonated aromatic carbons. These data are in agreement with those of the PMR spectrum. The singlets at δ 135.7, 137.7, 137.75, 140.3 (2C), 140.6 and 141.8 indicated the presence of non-protonated aromatic carbons. Thus the total of 7 singlets and 17 doublets account for the presence of four benzene nuclei in A. The singlet at δ 199.5 was assignable to the carbonyl carbon. The m/z 105 peak in the mass spectrum indicated the carbonyl group to be attached to a phenyl group. The structure of A was finally arrived at by the mechanistic path-way as proposed in Scheme 1.

That the conversion of a and A proceeds via the formation of c and a when the reaction product did not contain c even in traces. The final product A is formed by elimination of benzene molecule from the intermediate i as indicated in Scheme 1. This was confirmed by collecting the distillate from the reaction mixture whose UV spectrum showed absorptions at 245, 149, 155 and 261 nm.



SCHEME 1

Preparation of 2-methyl-4, 6-diphenylbenzophenone (A)

(a) A mixture of acetophenone (1 ml) and KOH (3 g) in diethylene glycol (50 ml) was refluxed in a round bottomed flask initially without condenser. When the reaction temperature rose above 160° the condenser was fitted and the mixture refluxed for 2 hr. It was cooled, diluted with water and extracted with ether. The ether layer was washed with water, dil. HCl and finally with water till neutral, dried (Na₂SO₄) and the solvent removed. The residue (0.5 g) was chromatographed over silica gel (25 g) column. Elution with petrol afforded A as a solid (0.2 g) which was crystallised from CHCl₃-MeOH, m.p. 185-86° (Found: C, 89.7; H, 5.7. C₂₆H₂₀O requires C, 89.6; H, 5.8%).

(b) A mixture of 1, 3-diphenyl-2-buten-1-one (c, 1 ml), acetophenone (a, 1 g) and KOH (3 g) in diethylene glycol (50 ml) was refluxed for 2 hr and worked-up as described above. The residue (0.9 g) was adsorbed over

silica gel (50 g) column and eluted with petrol to furnish A, m.p. 185-86° (CHCl₃-MeOH). It was identical (m.m.p. and co-IR) with A prepared from acetophenone only as mentioned above.

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Studies on Rutaceae: Part VIII†—Chemical Investigation on the Constituents of *Atalantia wightii* Tanaka, *Aegle marmelos* Correa ex Koen, *Ruta graveolens* Linn. & *Micromelum pubescens* Blume

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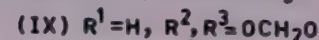
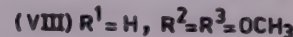
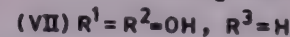
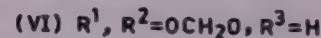
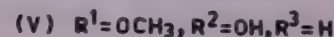
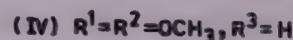
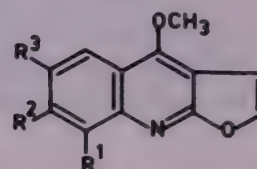
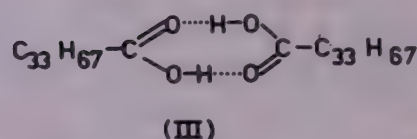
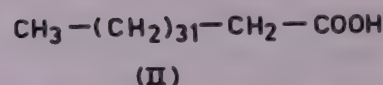
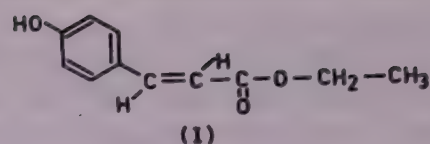
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A new phenolic ester, ethyl *p*-coumarate (I) and a long chain fatty acid, tetratriacontanoic acid (II) have been obtained from *Atalantia wightii* Tanaka. Skimmianine (IV) and haplopine (V), two major constituents of *Aegle marmelos* Correa ex Koen have been transformed to kokusagine (VI) a constituent of *Orixa japonica*, while kokusagine (VIII), isolated from *Ruta graveolens* Linn, has been converted into maculine (IX) a constituent of *Flindersia maculosa*. Several known coumarins have been isolated for the first time from *Micromelum pubescens* Blume.

The results of a systematic chemical investigation on the constituents of four species of Rutaceae belonging to the genera *Atalantia*, *Aegle*, *Ruta* and *Micromelum* are described in this note. All the new compounds isolated from these sources (Table 1) were characterised from their detailed spectral data and the known compounds by direct comparison (co-TLC, m.m.p. and co-IR) with authentic samples.

A new phenolic ester, ethyl *p*-coumarate (I)¹, C₁₁H₁₂O₃ (M⁺ 192), m.p. 62° (petrol-benzene) and a long chain fatty acid, tetratriacontanoic acid (II), C₃₄H₆₈O₂ (M⁺ 508), m.p. 75-76° (petrol-benzene) have been isolated from *A. wightii*. In the phenolic ester (I) the bathochromic shifts of the UV absorption maxima in alkali and the band at 3380 cm⁻¹ in its IR spectrum indicated the presence of a phenolic OH group. It formed an acetate, C₁₃H₁₄O₄ (M⁺ 234), m.p. 41° (petrol). I showed the presence of the *trans* double bond as revealed by the doublets at δ 7.56 and 6.20 (1H each, *J*=16.0 Hz; H-1' and H-2' respectively) in its 80 MHz PMR spectrum in CDCl₃. The second pair of doublets at δ 7.32 and 6.80 (2H each, *J*=8.0 Hz), forming an A₂B₂ system, clearly indicated two pairs of equivalent protons (H-2, H-6



and H-3 and H-5) and confirmed the presence of a *p*-disubstituted phenyl nucleus. The quartet at δ 4.20 (2H, *J*=7.0 Hz) and the triplet at δ 1.25 (3H, *J*=7.0 Hz) were attributed to the methylene protons attached to the ester oxygen and to the terminal methyl respectively.

The phenolic ester was subsequently synthesised from *p*-hydroxycinnamic acid and ethanol in the presence of concentrated sulphuric acid.

The ¹³C NMR spectrum in C₆D₆ of II appeared interesting. At moderate and high concentrations II existed as the dimer (III). Consequently the relaxation times (T₁'s) appeared longer going away from the carboxyl groups and were quite long at the end of the chains. The terminal methyl carbon appeared as a quartet at 14.3 ppm and the carboxyl carbon as a singlet at 179 ppm. The integrals of these carbons indicated the presence of only one carbonyl for each methyl. The triplets at 22.8, 24.8, 32.0 and 33.8 ppm were assigned to the methylene carbons C-33, C-3, C-32 and C-2 respectively on the basis of their peak intensities. The C-4 to C-31 carbons appeared in the region 29.0-30.0 ppm. (The number of car-

†Part VII: Banerji J, Das A K & Das B, *Heterocycles*, (In press)

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Table 1 — Identification of Constituents of Four Species of the Family Rutaceae*

Plant (Part)	Extract	Compound isolated	Yield (%)	m.p. °C (solvent)	Mol. formula (M†)
COUMARINS					
<i>Micromelum pubescens</i> Blume (Roots)	Petrol	Micromelummin	0.149	215 (benzene)	C ₁₅ H ₁₆ O ₆ (288)
		Phebalosin†	0.091	122 (benzene)	C ₁₅ H ₁₄ O ₄ (258)
		Imperatorin†	0.006	99 (benzene)	C ₁₆ H ₁₄ O ₄ (270)
		Angelical†	0.009	254 (benzene)	C ₁₁ H ₈ O ₄ (204)
		Limettin†	0.006	140 (benzene)	C ₁₁ H ₁₀ O ₄ (206)
		Scopoletin†	0.007	202 (benzene)	C ₁₀ H ₈ O ₄ (192)
	Ethanol	Minumicrolin†	0.008	132 (benzene)	C ₁₅ H ₁₆ O ₅ (276)
		Murrangatin†	0.011	132 (benzene)	C ₁₅ H ₁₆ O ₅ (276)
ALKALOIDS					
<i>Aegle marmelos</i> Correa ex Koen (Aerial part)	Ethanol	Skimmianine	0.007	176 (ethanol)	C ₁₄ H ₁₃ O ₄ N (259)
		Haplopine	0.001	203 (ethanol)	C ₁₃ H ₁₁ O ₄ N (245)
<i>Ruta graveolens</i> Linn (Aerial part)	Ethanol	Kokusaginine	0.002	170 (ethanol)	C ₁₄ H ₁₃ O ₄ N (259)
PHENOLIC ESTER					
<i>Atalantia wightii</i> Tanaka (Whole plant)	Ethanol	Ethyl <i>p</i> -coumarate†	0.002	62 (petrol-benzene)	C ₁₁ H ₁₂ O ₃ (192)
ALIPHATIC ACID					
	Chloroform	Tetratriacontanoic acid*	0.001	75-6 (petrol-benzene)	C ₃₄ H ₆₈ O ₂ (508)

*All the compounds gave satisfactory elemental analyses.

†Isolated for the first time from this genera.

‡New compound.

bons was deduced from the amplitude of the integral).

Skimmianine (IV) and haplopine (V), two major furoquinoline alkaloids of *Aegle marmelos* were transformed to kokusagine (VI), a constituent of *Orixa japonica*. On demethylation with boron tribromide in anhydrous methylene chloride at 0° both IV and V afforded 7,8-dihydroxydictamine (VII) which on a refluxing with bromochloromethane in dry acetone in the presence of anhydrous potassium carbonate afforded kokusagine (VI)².

Kokusaginine (VIII), a furoquinoline alkaloid isolated from *Ruta graveolens* Linn., was converted into maculine (IX), a constituent of *Flindersia maculosa*. On demethylation with boron tribromide in anhydrous methylene chloride at 0° VIII yielded 6,7-dihydroxydictamine (X) which on refluxing with bromochloromethane in dry acetone in

the presence of anhydrous potassium carbonate afforded IX³.

Melting points were recorded on a Kofler block apparatus and are uncorrected. Column chromatography and TLC were carried out with silica gel (60-120 mesh, BDH) and silica gel-G (Merck) respectively.

The chloroform extracted whole plant of *Atalantia wightii* (2 kg) was percolated with ethanol at 25° and the concentrate was treated with chloroform. The chloroform insoluble fraction was dissolved in chloroform-methanol (1:3) and chromatographed over silica gel. The benzene-ethyl acetate (1:1) eluate afforded the phenolic ester I (Found: C, 68.6, H, 6.3. C₁₁H₁₂O₃ requires C, 68.7; H, 6.3%); UV(EtOH): 212, 228 and 312 nm (log ε 4.12, 4.12 and 4.36); 211, 243, 311 and 368 nm (log ε 4.00, 3.98, 4.01 and 4.47); IR(KBr):

3380, 1680, 1630, 1600, 1580, 1510, 970 cm^{-1} ; MS: m/z 192 (M^+), 164, 147, 119.

I (10 mg) in dry pyridine (0.2 ml) with acetic anhydride (0.5 ml) (20° for 48 hr) afforded the acetate, m.p. 41 (petrol), yield 91% (Found: C, 66.6; H, 6.0. $\text{C}_{13}\text{H}_{14}\text{O}_4$ requires C, 66.7, H, 5.9%).

To a solution of *p*-hydroxycinnamic acid⁴ (1 g) in dry ethanol (15 ml) concentrated sulphuric acid (0.3 ml) was added and refluxed for 10 hr. The reaction mixture was cooled, diluted with water (100 ml), extracted with ether (3×100 ml), the ether layer successively washed with water (3×50 ml), saturated aq NaHCO_3 (3×50 ml) and water (3×100 ml) and dried. Ethyl *p*-coumarate (I) this obtained was purified by chromatography over silica gel followed by crystallisation, yield 85%.

Skimmianine (IV, 200 mg) was dissolved in anhydrous methylene chloride (20 ml) and the solution was cooled at 0° . Boron tribromide (2 ml) diluted with methylene chloride (10 ml) was added dropwise under nitrogen atmosphere with vigorous stirring. The reaction was continued for 2 hr and then kept for 10 hr at room temperature. The reaction mixture was added to ice-cold water (100 ml), left for 2 hr, extracted with methylene chloride (4×50 ml), washed with aq 2% NaHCO_3 (3×50 ml) and water (3×50 ml) and dried. The concentrated solution yielded 7,8-dihydroxydictamine (VII) which crystallised from ethanol, m.p. 265° (d), yield 68% (Found: C, 62.5; H, 3.9; N, 6.1. Calc. for $\text{C}_{12}\text{H}_9\text{O}_4\text{N}$: C, 62.3; H, 3.9, N, 6.0%).

Following the same procedure haplopinine (V, 200 mg) was demethylated with boron tribromide (2 ml) to get VII, m.p. and m.m.p. 265° ; yield 72%.

7,8-Dihydroxydictamine (VII, 100 mg) was dissolved in dry acetone (30 ml) to which anhydrous

potassium carbonate (1 g) was added. Bromochloromethane (0.5 ml) was subsequently added and the mixture refluxed for 20 hr. It was filtered and concentrated when a gummy solid was obtained. The solid was dissolved in benzene and the solution on concentration yielded kokusagine² (VI), m.p. $197-98^\circ$ (lit² m.p. 201) yield 43% (Found: C, 64.3; H, 3.7; N, 5.9. Calc. for $\text{C}_{13}\text{H}_9\text{O}_4\text{N}$: C, 64.2; H, 3.7; N, 5.7%); MS: m/z 243 (M^+).

Kokusaginine (Vi, 200 mg) was demethylated with boron tribromide (2 ml) following the same procedure as described for the demethylation of skimmianine (IV). The product, 6,7-dihydroxydictamine (X) was crystallised from ethanol, m.p. 262° (d), yield 61% (Found: C, 62.1; H, 3.8; N, 6.2. Calc. for $\text{C}_{12}\text{H}_9\text{O}_4\text{N}$: C, 62.3, H, 3.9; N, 6.0%).

6,7-Dihydroxydictamine ($\times 100$ mg) was reacted with bromochloromethane (0.5 ml) in the presence of anhydrous potassium carbonate (1 g) following the same procedure as described above for the conversion of VII to VI. The reaction product, maculine (IX)³, was isolated in 38%, yield m.p. 194° (methanol) (lit.³ m.p. $196-97^\circ$) (Found: C, 64.1; H, 3.6; N, 5.6. Calc. for $\text{C}_{13}\text{H}_9\text{O}_4\text{N}$: C, 64.2, H, 3.7; N, 5.8%).

The authors wish to express sincere thanks to Mr A K Acharya, Mr P Ghos and Mr J Ghosh of the Organic Instrumentation Laboratory of our Department for spectral measurements and to the UGC, New Delhi for financial assistance.

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Isolation of 4,4'-Dimethoxy-*trans*-stilbene & Flavonoids from Leaves & Twigs of *Vitex negundo* Linn.

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The leaves and twigs of *Vitex negundo* Linn. afford a stilbene derivative characterised as 4,4'-dimethoxy-*trans*-stilbene (1), along with five flavones, 5,6,7,8,3',4',5'-heptamethoxy (2), 5-hydroxy-6,7,8,3',4'-pentamethoxy (5-O-desmethylnobiletin) (3), 5-hydroxy-6,7,8,3',4',5'-hexamethoxy (gardenin A) (4), 5-hydroxy-6,7,8,4'-tetramethoxy (gardenin B) (5) and 5-hydroxy-7,3',4',5'-tetramethoxyflavone (corymbosin) (6). This is the first report of 1 as a natural product. Compound 1 has been converted into 3,6-dimethoxyphenanthrene (11). The flavones 2, 5 and 6 undergo interesting rearrangements when treated with hydrazine hydrate to generate the pyrazoles 14, 15 and 16 respectively.

Vitex negundo Linn. (fam. Verbenaceae) has been used in the Indian medicinal system as a febrifuge, lactagogue and emmenagogue¹. Recent work on the petrol extract of this plant has revealed its efficacy in the treatment of acute rheumatoid arthritis². This necessitated a reinvestigation of the chemical constituents of the plant in order to isolate the active compounds.

Careful chromatography of the petrol extract of the leaves and twigs of *Vitex negundo* Linn. over silica gel yielded the stilbene derivative, 4,4'-dimethoxy-*trans*-stilbene (1), C₁₆H₁₆O₂ (M⁺ 240), m.p. 212° (C₆H₆), yield 0.005%, together with five known flavones, 5,6,7,8,3',4',5'-heptamethoxyflavone (2)³ (0.004%), 5-hydroxy-6,7,8,3',4'-pentamethoxyflavone (5-O-desmethylnobiletin) (3)⁴ (0.001%), 5-hydroxy-6,7,8,3',4',5'-hexamethoxyflavone (gardenin A) (4)⁵ (0.002%), 5-hydroxy-6,7,8,4'-tetramethoxyflavone (gardenin B) (5)⁶ (0.004%) and 5-hydroxy-7,3',4',5'-tetramethoxyflavone (corymbosin) (6)⁷ (0.005%). This is the first report of the isolation of 1 from a natural source. It had been earlier obtained as a synthetic product⁸. The flavones have also been isolated for the first from this plant.

The UV spectrum of 1 in EtOH [212 (log ε, 3.88), 306 (4.12) and 3.25 (4.11)] indicated *trans* configuration of the olefinic double bond. The 400 MHz PMR and 100 MHz ¹³C NMR spectra of 1 suggested the

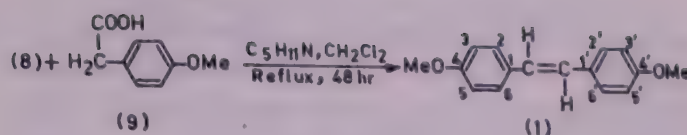
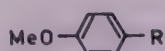
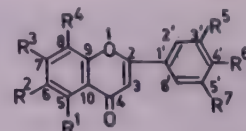


Chart 1



(7) R = COOH

(8) R = CHO



(2) R¹ = R² = R³ = R⁴ = R⁵ = R⁶ = R⁷ = OMe

(3) R¹ = OH, R² = R³ = R⁴ = R⁵ = R⁶ = OMe, R⁷ = H

(4) R¹ = OH, R² = R³ = R⁴ = R⁵ = R⁶ = R⁷ = OMe

(5) R¹ = OH, R² = R³ = R⁴ = R⁶ = OMe, R⁵ = R⁷ = H

(6) R¹ = OH, R³ = R⁵ = R⁶ = R⁷ = OMe, R² = R⁴ = H

(12) R¹ = R² = R³ = R⁴ = R⁶ = OMe, R⁵ = R⁷ = H

(13) R¹ = R² = R⁵ = R⁶ = R⁷ = OMe, R³ = R⁴ = H

symmetrical nature of the molecule. On oxidation with alkaline potassium permanganate 1 produced anisic acid (7). The synthesis of 1 was achieved by a simple and different route to that reported by Findlay *et al.*⁸ The synthetic product, m.p. 212° was found to be identical (m.m.p., co-TLC and co-IR) with the natural sample (Chart 1).

4,4'-Dimethoxy-*trans*-stilbene (1) was irradiated in ethanol containing a trace of iodine with a medium pressure mercury vapour lamp for 12 hr when 3,6-dimethoxyphenanthrene (11) was isolated and characterised by its PMR spectrum. It appears that compound 1 first photochemically isomerises to the less stable *cis*-form 10 which then undergoes photocyclisation to afford 11 (Chart 2).

Partial demethylation of 5,6,7,8,3',4',5'-heptamethoxyflavone (2) by heating with aluminium chloride in ether gave gardenin A (4), which on methylation with dimethyl sulphate gave 2.

Gardenin B (5) on methylation with dimethyl sulphate afforded 5,6,7,8,4'-pentamethoxyflavone (12), previously isolated from *Citrus jambhiri*⁹.

Methylation of corymbosin (6) with dimethyl sulphate gave 5,7,3',4',5'-pentamethoxyflavone (13), previously isolated from the fruits of *Merrillia caloxylon*¹⁰.

The flavones 2, 5 and 6 when treated with hydrazine hydrate in ethanol underwent an interesting rearrangement producing the pyrazole derivative 14, 15 and 16 respectively (Chart 3), the structures of which were settled on the basis of their IR and PMR spectral data.

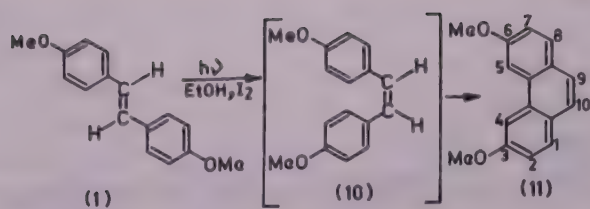
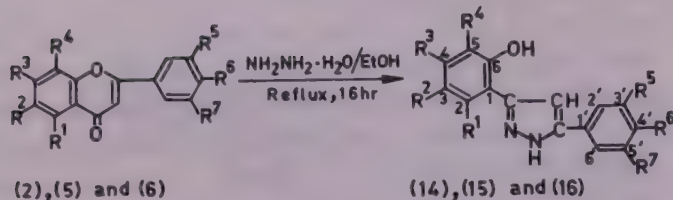


Chart 2



- (2) and (14) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = \text{OMe}$
 (5) and (15) $R^1 = \text{OH}, R^2 = R^3 = R^4 = R^6 = \text{OMe}, R^5 = R^7 = \text{H}$
 (6) and (16) $R^1 = \text{OH}, R^3 = R^5 = R^6 = R^7 = \text{OMe}, R^2 = R^4 = \text{H}$

Chart 3

The isolation of flavones and the stilbene derivative from the same plant is biogenetically significant as both systems are biosynthesised from phenylpropanoid units derived from the shikimate pathway¹¹.

The melting points were recorded on a Kofler block apparatus and are uncorrected. Column chromatography was carried out with silica gel (BDH, 60-120 mesh) and TLC with silica gel G (E. Merck). All the compounds gave satisfactory elemental analyses.

The leaves and twigs of *V. negundo* were collected from Ranchi, Bihar (India). The air-dried and powdered leaves and twigs (10 kg) were extracted with petroleum ether (60-80°) for 48 hr in a soxhlet apparatus. The extract was concentrated and chromatographed over silica gel.

4,4'-Dimethoxy-trans-stilbene (1)

Chromatography of the concentrate of the petrol extract gave from the earlier part of the benzene eluate **1**, which crystallised from benzene as white needles, yield 515 mg, m.p. 212°, IR (KBr): 1610, 1570, 1510, 1460, 1260, 1240, 1210, 830 cm^{-1} ; PMR (CDCl_3): δ 7.40 (4H, d, $J = 10.0$ Hz, H-2, H-6, H-2' and H-6'), 6.85 (4H, d, $J = 10.0$ Hz, H-3, H-5, H-3' and H-5'), 6.95 (2H, s, $\text{CH}=\text{CH}$) and 3.80 (6H, s, $2 \times \text{OCH}_3$); ^{13}C NMR (CDCl_3): δ 158.04 (C-4 and C-4'), 131.46 (C-1 and C-1'), 128.43 (C-2, C-6, C-2' and C-6'), 114.07 (C-3, C-5, C-3' and C-5'), 127.21 ($\text{C}=\text{C}$) and 55.98 ($2 \times \text{OCH}_3$); MS: m/z 240 (M^+), 225, 165, 120.

5,6,7,8,3',4',5'-Heptamethoxyflavone (2)

The later fractions of the benzene eluate gave a sol-

id which crystallised from benzene as pale yellow needles of **2**, yield 420 mg, m.p. 105°.

5-Hydroxy-6,7,8,3',4'-pentamethoxyflavone (5-O-desmethylnobiletin) (3) and 5-hydroxy-6,7,8,3',4',5'-hexamethoxyflavone (gardenin A) (4)

Flavones **3** and **4** were isolated from the earlier part of the benzene-ethyl acetate (4:1) eluate and were separated by repeated column chromatography oversilica gel. 5-Hydroxy-6,7,8,3',4'-pentamethoxyflavone (5-O-desmethylnobiletin) (**3**) was crystallised from EtOH as light yellow prisms, yield 98 mg, m.p. 145°.

5-Hydroxy-6,7,8,3',4',5'-hexamethoxyflavone (gardenin A) (**4**) was crystallised from EtOH as light yellow needles, yield 195 mg, m.p. 159°.

5-Hydroxy-6,7,8,4'-tetramethoxyflavone (gardenin B) (5)

The later fractions of the benzene-ethyl acetate (4:1) eluate afforded **5** which crystallised from benzene as light yellow prisms yield 410 mg, m.p. 180°.

5-Hydroxy-7,3',4',5'-tetramethoxyflavone (corymbosin) (6)

The solid obtained from the benzene-ethyl acetate (1:1) eluate was crystallised from benzene to give **6** as yellow needles, yield 525 mg, m.p. 188°.

Synthesis of 4,4'-dimethoxy-trans-stilbene (1)

A mixture of 4-methoxybenzaldehyde (**8**) (1.5 g) and 4-methoxyphenylacetic acid (**9**) (1.5 g) was dissolved in dry CH_2Cl_2 (50 ml). Piperidine (0.25 ml) was added and the mixture was refluxed on a water-bath for 16 hr. The mixture was cooled, filtered and extracted first with 5% HCl (3×50 ml) followed by 5% aq NaOH (3×50 ml). The CH_2Cl_2 layer was washed with water (3×50 ml) and evaporated to yield a gummy mass which was chromatographed over silica gel. The benzene-ethyl acetate (4:1) eluate gave a solid which crystallised from benzene as white needles of 4,4'-dimethoxy-trans-stilbene (**1**), yield 750 mg, m.p. 212°; IR (KBr): 1610, 1570, 1510, 1460, 1260, 1240, 1210, 830 cm^{-1} .

Conversion of 1 into 3,6-dimethoxyphenanthrene (11)

Compound (**1**) (50 mg) in EtOH (100 ml) containing a trace of I_2 was irradiated with medium pressure Hg vapour lamp for 12 hr. The product after usual work-up was purified by column chromatography over silica gel. The ethyl acetate eluate afforded **11**, yield 20 mg, m.p. 168° (benzene); UV (EtOH): 293, 281, 257 and 212 nm ($\log \epsilon$ 4.15, 4.10, 4.85 and 4.60 respectively); IR (KBr): 1610, 1495, 1450, 1140, 810 cm^{-1} .

Reaction of Flavones with hydrazine hydrate

5,6,7,8,3',4',5'-Heptamethoxyflavone (**2**) (20 mg) was dissolved in EtOH (10 ml) and hydrazine hydrate (10 ml) was added. The mixture was refluxed on a water-bath for 14 hr, concentrated and diluted with water (10 ml). The pyrazole derivative **14** which precipitated was filtered, washed with water, dried and crystallised from benzene as white needles, yield 15 mg, m.p. 99-101°, IR (KBr): 3300, 1630, 1585, 1500, 1460, 1260, 1125, 800 cm^{-1} ; PMR (CDCl_3): δ 6.80 (1H, s, =C-CH=), 7.15 (2H, s, H-2' and H-6'), 3.93, 3.87 (3H, each, s, OCH_3), 3.82 (15H, s, $5 \times \text{OCH}_3$), MS: m/z 446 (M^+), 431, 386, 279, 167.

Following the same procedure 5-hydroxy-6,7,8,4'-tetramethoxyflavone (gardenin B) (**5**) (20 mg) and 5-hydroxy-7,3',4',5'-tetramethoxyflavone (corymbosin) (**6**) (20 mg) were reacted with hydrazine hydrate. Flavone **5** afforded **15**, yield 13 mg, m.p. 110°, IR (KBr): 3400, 1640, 1590, 1500, 1460, 1260, 1120, 810 cm^{-1} ; PMR (CDCl_3): δ 6.75 (1H, s, =C-CH=), 7.15 (2H, d, $J=8.9$ Hz, H-2' and H-6'), 6.45 (2H, d, $J=8.9$ Hz, H-3' and H-5'), 3.80 (9H, s, $3 \times \text{OCH}_3$), MS: m/z 372 (M^+), 357, 312, 205, 107.

Flavone **6** produced the pyrazole derivative **16**, yield 12 mg, m.p. 105°, IR (KBr): 3400, 1650, 1450, 1260, 1120, 800 cm^{-1} ; PMR (CDCl_3): δ 7.00 (1H, s,

=C-CH=), 7.08 (2H, s, H-2' and H-6'), 6.61 (1H, d, $J=2.0$ Hz, H-5), 6.22 (1H, d, $J=2.0$ Hz, H-3), 3.92 (6H, s, $2 \times \text{OCH}_3$), 3.80 and 3.76 (3H, each, s, OCH_3); MS: m/z 372 (M^+), 357, 312, 205, 167.

The authors express their sincere thanks to Mr A K Acharya, Mr P Ghose and Mr J Ghosh of the Organic Instrumentation Laboratory, Department of Chemistry, Calcutta University, for spectral measurements and to the UGC, New Delhi for financial assistance.

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Products Active on Mosquitoes: Part II† – Synthesis of Biologically Active Diethers of 3,7-Dimethyl-1,8-octanediol‡

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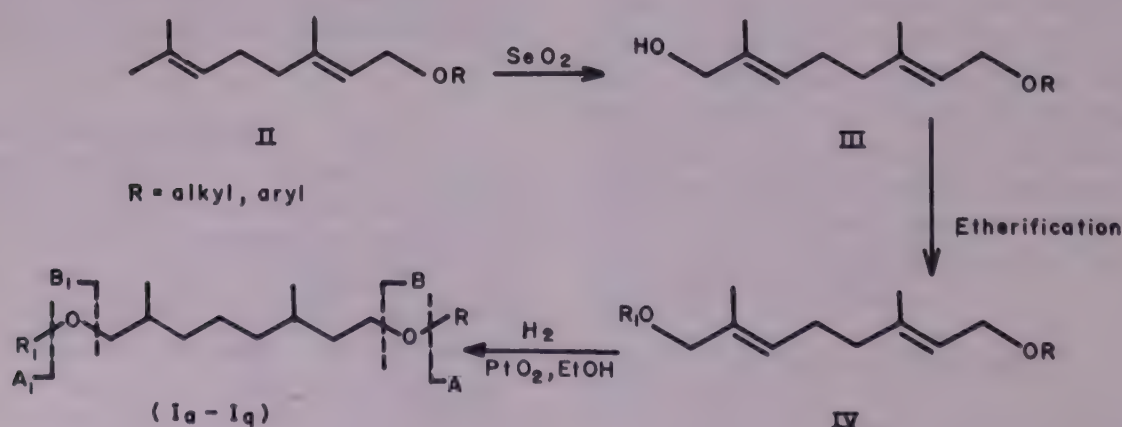
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Seventeen compounds (Ia-Iq) of the series 1-benzyloxy/phenoxy-8-alkoxy- and 1-alkoxy-8-benzyloxy/phenoxy-octanes have been synthesized. Most of them show multiple biological activity on mosquitoes, including juvenile hormonal activity.

Juvenile hormone analogues (JHAs) are prominent among insect bioregulators as chemicals with distinct potential as well as limitations as pest control agents. Some JHAs have found commercial application in special situations and strategies. This is particularly true where the adult insect acquires the damaging stage, e.g. manure breeding flies, stored grain pests flood water mosquitoes etc.¹ Terpenoid aryl² as well as alkyl³ monoethers have been shown to possess juvenile hormonal activity. Unsaturated alkyl aryl mixed diethers of the type IV also exhibit JH activity on mosquitoes and red cotton bugs⁴. With a view to studying the effect of saturation of double bonds on biological activity we have now prepared saturated diethers, 1-benzyloxy/phenoxy-8-alkoxy- and 1-alkoxy-8-benzyloxy/phenoxy-1,8-octanes (Ia-Iq).

The required unsaturated diethers (IV) were prepared by oxidizing geranyl monoethers (II) with sele-

mium dioxide, followed by etherification of the resulting 8-hydroxygeranyl monoethers (III)⁴ in the presence of sodium hydride and DMSO. The saturated diethers (Ia-Iq) were obtained by hydrogenation of IV in the presence of Adam's catalyst in ethanol (Scheme 1). Yields, boiling points and characteristic PMR data of the compounds (Ia-Iq) are given in Table 1. Compounds with R as alkyl or benzyl exhibit a triplet of C-1 methylene at δ 3.1-3.4 which is shifted to 3.6-3.9 when R is phenyl. Similarly, the doublet of C-8 methylene which appears at δ 3.01-3.4 when R₁ is alkyl or benzyl is shifted downfield (3.6-3.9) when R is phenyl. Secondary methyls at C-3 and C-7 give a doublet at δ 0.81-0.9 ($J=6$ Hz). All the saturated diethers except Ie give rise to molecular ion (M^+) with a relative intensity ranging from 1% to 91% upon electron bombardment. Most of the fragments arise due to cleavage α to the oxygen atom which is diagnostic of ether linkage. In compounds where R (R₁) is benzyl, benzylic cleavage appears to get preference over the cleavage of C₁-O (or C₈-O) bond giving rise to fragment A(A₁) (trophylum ion) as the base peak (Table 2). Compounds with phenoxy group at C-1 (or C-8) produce fragment B(B₁) due to fission of C₁-O (or C₈-O) bond. Hydrogen transfer to oxygen in fragment B(B₁) produces phenol ion which forms the base peak. Fragments $M^+ - A$ (A₁) or $M^+ - B$ (B₁) are not observed, probably because the other end of the molecule possesses an ether linkage which also cleaves simultaneously. All the compounds gave satisfactory elemental analysis.



SCHEME 1

†NCL Communication No. 4178

‡Paper appearing in Pesticide Science (1987; in press) should be treated as Part I.

Table 1—Yields, Boiling Points and PMR Data of the Compounds (Ia-Iq)

Compd	R	R ₁	Yield (%)	b.p.* °C/0.3-0.5	C ₁ -H ₂ (t, J=6)	C ₈ -H ₂ (d, J=6)	-OMe (s)	-OCH ₂ CH ₃ (q, J=6)	-OCH ₂ CH ₃ (t, J=6)	Benzyllic -CH ₂ (s)	Aromatic -CH ₃ (s)
Ia	Bz	Bz	94	165-170	3.43	3.17	—	—	—	4.33	—
Ib	Bz	Me	93	160-170	3.36	3.08	3.2	—	—	4.33	—
Ic	Bz	Et	85	150-160	3.46	3.16	—	3.41	0.96	4.45	—
Id	Et	Bz	95	140-150	3.26†	4.5	—	3.26	0.93	4.4	—
Ie	Me	Bz	95	140-150	3.36	4.5	3.26	—	—	4.6	—
If	p-Me-Bz	Me	79	160-170	3.33	3.05	3.16	—	—	4.26	2.26
Ig	p-Me-Bz	Et	81	150-160	3.36	3.11	—	3.33	0.9	4.33	2.31
Ih	Ph	Me	84	150-155	3.66	3.48	3.03	—	—	—	—
Ii	Ph	Et	69	140-145	3.9	3.1	—	3.31	0.91	—	—
Ij	Me	Ph	95	150-160	3.3	3.68	3.25	—	—	—	—
Ik	Me	p-Me-Bz	97	145-155	3.25	3.30	3.31	—	—	4.43	2.36
Il	Et	Ph	78	150-155	3.40†	3.78	—	3.40†	0.95	—	—
Im	Et	p-Me-Bz	81	150-160	3.23	3.43	—	3.28	0.95	4.43	4.38
In	Me	p-Me-Bz	79	160-165	3.3	3.75	3.06	—	—	—	2.03
Io	Et	p-Me-Ph	78	160-170	3.3†	3.68	—	3.3†	0.9	—	2.16
Ip	Me	p-Cl-Ph	79	160-170	3.25	3.66	3.25	—	—	—	—
Iq	Et	p-Cl-Ph	51	170-180	3.43†	3.80	—	3.43†	1.06	—	—

Chemical shifts are in δ , ppm for CCl₄ solutions and *J* values in Hz.

*Bath temperature.

†Multiplet of 4 protons.

Table 2—Significant Fragments of the Compounds (Ia-Iq)

Fragment (<i>m/z</i>) (relative abundance %)					Fragment (<i>m/z</i>) (relative abundance, %)				
Compd.	Mol. formula	M ⁺	A(A1)	B(B1)	Compd.	Mol. formula	M ⁺	A(A1)	B(B1)
Ia	C ₂₄ H ₃₄ O ₂	354 (1)	91 (100)	107 (—)	Ij	C ₁₇ H ₂₈ O ₂	264 (20)	77 (8)	94* (100)
Ib	C ₁₈ H ₃₀ O ₂	278 (7.5)	91 (100)	107 (38)	Ik	C ₁₉ H ₃₂ O ₂	292 (6)	105 (100)	121 (55)
Ic	C ₁₉ H ₃₂ O ₂	292 (2)	91 (100)	107 (38)	Il	C ₁₈ H ₃₀ O ₂	278 (7)	77 (9)	94* (100)
Id	C ₁₉ H ₃₂ O ₂	292 (4)	91 (100)	107 (10)	Im	C ₂₀ H ₃₄ O ₂	306 (3)	105 (100)	171 (19)
Ie	C ₁₈ H ₃₀ O ₂	248 (5)	105 (100)	107 (50)	In	C ₁₈ H ₃₀ O ₂	278 (23)	91 (18)	108* (100)
If	C ₂₀ H ₃₂ O ₂	292 (5)	105 (100)	121 (54)	Io	C ₁₉ H ₃₂ O ₂	292 (50)	91 (14)	108* (100)
Ig	C ₂₀ H ₃₄ O ₂	306 (5)	105 (100)	121 (54)	Ip	C ₁₇ H ₂₇ O ₂ Cl	298 (12)	111 (15)	128* (100)
Ih	C ₁₇ H ₂₈ O ₂	264 (72)	77 (35)	94* (100)	Iq	C ₁₈ H ₂₉ O ₂ Cl	312 (30)	111 (14)	128* (100)
Ii	C ₁₈ H ₃₀ O ₂	278 (91)	77 (48)	94* (100)					

*Phenol ion

The compounds were extensively tested in laboratory and field simulated conditions for different biological activities on different insects, pests and vectors. Apart from JH activity, shown by most of the compounds, many also exhibited toxicity and deterred oviposition. Some of the compounds were sufficiently active (at 0.05 ppm) to warrant further evaluation and studies on persistence etc. under simulated field con-

ditions. Detailed results of these bioevaluations form part of a separate publication.

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Synthesis & Pharmacological Activities of 5-(Aminoacetyl-amino)-4-carbethoxy- 1-phenylpyrazoles

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A number of new 5-(aminoacetyl-amino)-4-carbethoxy-1-phenyl-pyrazoles have been prepared and screened for their pharmacological activities. Some of these compounds exhibit significant analgesic and antiinflammatory activities.

5-Aminopyrazoles exhibit a variety of biological activities¹⁻⁵. 5-Acylaminopyrazoles are reported to possess tranquilizing, analgesic and other pharmacodynamic properties⁶. It was, therefore, thought of interest to synthesise 5-acylamino-4-carbethoxy-1-phenylpyrazoles (5-21) and evaluate their pharmacological activities.

The 5-aminopyrazoles⁷⁻⁸ (3), required as the starting materials, were prepared by the reaction of phenylhydrazine with ethyl ethoxycyanoacetate (2a) or ethyl(bis-methylthio)methylenecyanoacetate⁹ (2b) (Scheme 1).

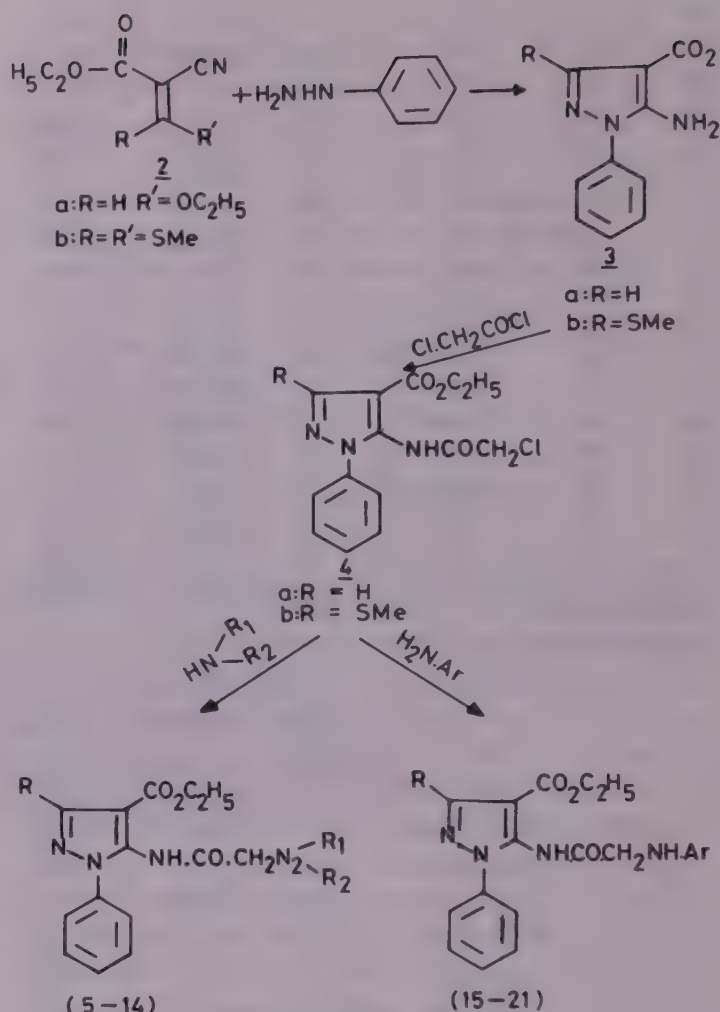
The reaction of aminopyrazoles (3) in refluxing chloroform with excess of chloroacetyl chloride furnished the corresponding chloroacetyl derivatives (4) in satisfactory yields. The 5-chloroacetyl-amino-4-carbethoxy-1-phenylpyrazoles (4) on reaction with secondary amines in refluxing benzene gave 5-14, while 5-arylaminoacetylaminopyrazoles (15-21) were obtained when respective arylamines were reacted with 4 in refluxing ethanol. The structures of 5-21 (Table 1) were established by elemental analyses and UV and IR spectral data.

Biological activity

Compounds 4-14, 16, 18 and 21 were screened for their anti-inflammatory¹⁰ and analgesic¹¹ activities using aspirin as standard at a dose of 400 mg/kg p.o. The pyrazoles 5 and 10* showed 50%, while compounds 8 and 9* exhibited 40% anti-inflammatory activity as compared with aspirin.

The compounds 9*, 10 and 12* exhibited significant analgesic activity in comparison to aspirin.

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*As hydrochloride salt



Scheme 1

The compounds 9* and 12* possessed the maximum analgesic activity (80% of aspirin) among the tested compounds and 9* and 12* were equipotent. Compound 13* exhibited 40% analgesic activity at 10 mg/kg p.o.

The compounds 8, 9* and 10 possessed both antiinflammatory and analgesic activities.

The LD_{50} values¹² of compounds 9*, 10, and 12* were found to be 2.00 ± 0.25 ; 1.00 ± 0.125 ; and 2.00 ± 0.2 g/kg p.o. respectively.

5-Chloroacetyl-amino-4-carbethoxy- 1-phenylpyrazole (4a)

A mixture of 5-amino-4-carbethoxy-1-phenylpyrazole (3a) (11.55 g, 0.05 mol) and chloroacetyl chloride (11.3 g, 0.1 mol) in chloroform (100 ml) was refluxed on a water-bath for 6 hr, and solvent recovered under reduced pressure. The residue was poured over crushed ice, filtered, washed with saturated sodium bicarbonate solution and water, dried and crystallized from ethanol to give 4a as

Table 1—Characterisation Data of Various 5-(Substituted aminoacylamino)-4-carbethoxy-1-phenylpyrazoles (5-21)

Compd	R	$-N\begin{smallmatrix} R_1 \\ R_2 \end{smallmatrix}$	Yield (%)	Crystallized from*	m.p. °C	Mol. formula	Found (%) (Calc.)	
							C	H
5	H	Diethylamino	57	H	93-94	$C_{18}H_{24}N_4O_3$	62.6 (62.8)	7.3 (7.0)
6	H	Pyrrolidino	48	Cy	116-18	$C_{18}H_{22}N_4O_3$	63.0 (63.2)	6.4 (6.4)
7	H	Piperidino	56	Pr-W	96-98	$C_{19}H_{24}N_4O_3$	64.2 (64.0)	7.0 (6.7)
8	H	N-Methylpiperazino	46	Cy	132-34	$C_{19}H_{25}N_5O_3$	61.6 (61.5)	7.1 (6.7)
9	H	Morpholino	63	Pr-W	132-33	$C_{18}H_{22}N_4O_4$	60.3 (60.3)	6.2 (6.1)
10	-SCH ₃	Diethylamino	65	Pr-W	105-7	$C_{19}H_{26}N_4O_3S$	58.8 (58.5)	6.7 (6.7)
11	-SCH ₃	Pyrrolidino	54	Pr-W	137-38	$C_{19}H_{24}N_4O_3S$	58.6 (58.8)	6.2 (6.2)
12	-SCH ₃	Piperidino	60	Pr-W	148-49	$C_{20}H_{26}N_4O_3S$	59.6 (59.7)	6.5 (6.5)
13	-SCH ₃	N-Methylpiperazino	67	Cy	140-42	$C_{20}H_{27}N_5O_3S$	57.9 (57.6)	6.7 (6.5)
14	-SCH ₃	Morpholino	70	Pr-W	141-42	$C_{19}H_{24}N_4O_4S$	56.6 (56.4)	6.2 (5.9)
15	H	3-Methyl anilino	42	Cy-B	145-46	$C_{21}H_{22}N_4O_3$	66.5 (66.7)	5.7 (5.8)
16	-H	4-Methyl anilino	45	Cy	148-49	$C_{21}H_{22}N_4O_3$	66.7 (66.7)	6.0 (5.8)
17	-H	4-Methoxy anilino	58	Cy	146-48	$C_{21}H_{22}N_4O_4$	63.8 (64.0)	5.5 (5.6)
18	-H	4-Chloro anilino	62	Cy	183-85	$C_{20}H_{19}N_4O_3Cl$	60.0 (60.2)	4.8 (4.8)
19	-H	2,6-Dichloro anilino	41	Cy	106-8	$C_{20}H_{18}N_4O_3Cl_2$	55.4 (55.4)	4.1 (4.2)
20	-SCH ₃	Anilino	42	Cy	149-52	$C_{21}H_{22}N_4O_3S$	61.6 (61.5)	5.6 (5.4)
21	-SCH ₃	4-Methyl anilino	42	Cy	149-52	$C_{22}H_{24}N_4O_3S$	62.0 (62.3)	5.7 (5.7)

*H-Hexane; Cy = cyclohexane; Pr = propanol; W = water; B = benzene

colourless crystals, yield 72%, m.p. 114-15° (Found: C, 54.74; H, 4.66. $C_{14}H_{14}N_3O_3Cl$ requires C, 54.63; H, 4.55); λ_{max} (EtOH): 243 nm; IR: 3140 (-NH), 1710, 1670, 1590, 1510 cm^{-1} .

Similarly, compound **4b** was prepared by the reaction of 5-amino-4-carbethoxy-3-methylthio-1-phenylpyrazole (**3b**) and chloroacetyl chloride. It was recrystallized from isopropanol-water as colourless crystals, yield 82%, m.p. 160-61° (Found: C, 51.20; H, 4.72. $C_{15}H_{16}N_3O_3S$ requires C, 50.92; H, 4.53); λ_{max} (EtOH): 239 nm; IR: 3140 (-NH), 1710, 1670, 1590, 1510 cm^{-1} .

4-Carbethoxy-5-(morpholinoacetyl-amino)-1-phenylpyrazole (**9**)

A mixture of **4a** (0.01 mol) and morpholine (0.02 mol) in dry benzene (50 ml) was refluxed on

a water-bath for 8 hr, cooled, diluted with benzene (50 ml) and filtered. The filtrate was washed with water, dried (anhydr. Na_2SO_4) and solvent removed *in vacuo*. The crude product was crystallized from isopropanol-water to give **9** as colourless crystals, m.p. 132-33°; UV(EtOH): 243 nm; IR: 3300 (-NH), 1720 (C=O) cm^{-1} ; MS: m/z 358 (M^+), 313, 273, 232, 227, 212, 198, 184, 127, 101, 99, 91, 86, 77.

Similarly, compounds **5-8**, **10-14** were obtained by reacting either **4a** or **4b** with secondary amines in refluxing benzene, while compounds **15-21** were obtained from **4a** or **4b** with primary amines in refluxing ethanol.

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